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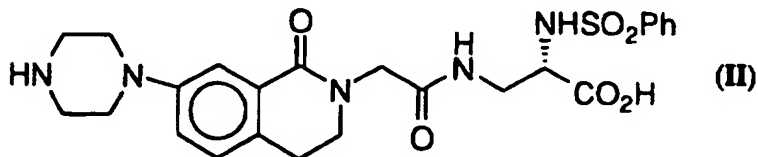
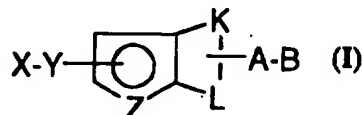
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(54) Title: FIBRINOGEN RECEPTOR ANTAGONISTS

(57) Abstract

Fibrinogen receptor antagonists having formula (I), for example (II).



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TITLE OF THE INVENTION**FIBRINOGEN RECEPTOR ANTAGONISTS****BACKGROUND OF THE INVENTION**

5 The invention relates generally to modulating cell adhesion and to inhibiting the binding of fibrinogen and other proteins to blood platelets, and inhibiting the aggregation of blood platelets specifically to the gp IIb/IIIa fibrinogen receptor site. Fibrinogen is a glycoprotein present in blood plasma that participates in platelet aggregation and in
10 fibrin formation. Platelets are cell-like anucleated fragments, found in the blood of all mammals, that also participate in blood coagulation. Interaction of fibrinogen with the IIb/IIIa receptor site is known to be essential for normal platelet function.

 When a blood vessel is damaged by an injury or other
15 causative factor, platelets adhere to the disrupted subendothelial surface. The adherent platelets subsequently release biologically active constituents and aggregate. Aggregation is initiated by the binding of agonists, such as thrombin, epinephrine, or ADP to specific platelet membrane receptors. Stimulation by agonists results in exposure of
20 latent fibrinogen receptors on the platelet surface, and binding of fibrinogen to the glycoprotein IIb/IIIa receptor complex.

 Attempts have been made to use natural products and synthetic peptides to determine the mechanism of adhesion and platelet aggregation. For example, Rouslahti and Pierschbacher in Science, 238,
25 491-497 (1987), describe adhesive proteins such as fibronectin, vitronectin, osteopontin, collagens, thrombospondin, fibrinogen, and von Willebrand factor that are present in extracellular matrices and in blood. The proteins contain the tripeptide arginine-glycine-aspartic acid (RGD) as their glycoprotein IIb/IIIa recognition site. These arginine-glycine-
30 aspartic acid containing tripeptides are recognized by at least one member of a family of structurally related receptors, integrins, which are heterodimeric proteins with two membrane-spanning subunits. The authors state that the conformation of the tripeptide sequence in the individual proteins may be critical to recognition specificity.

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Cheresh in Proc. Nat'l Acad. Sci. U.S.A., 84, 6471-6475, (1987), describes an Arg-Gly-Asp directed adhesion receptor expressed by human endothelial cells that is structurally similar to the IIb/IIIa complex on platelets but is antigenically and functionally distinct. This
5 receptor is directly involved in endothelial cell attachment to fibrinogen, von Willebrand factor, and vitronectin.

Pierschbacher and Rouslahti, in J. Biol. Chem., 262, (36), 17294-17298 (1987) hypothesized that the Arg-Gly-Asp sequence alone would be a sufficient signal for receptor recognition and binding and that,
10 therefore, the conformation of the tri-peptide sequence would be determinative. Various synthetic peptides were produced and the authors concluded that the stereochemical conformation of Arg-Gly-Asp as influenced by enantiomeric substitutions or additions to this sequence significantly influenced receptor-ligand interaction. The authors further
15 showed that cyclization of a decapeptide by forming a disulfide bridge between non-terminal residues Pen and Cys, rendered the peptide much less effective at inhibiting attachment to fibronectin.

In Proc. Nat'l Acad. Sci. U.S.A., 81, 5985-5988 (1984), the same authors describe tetrapeptide variants of the cell recognition site of
20 fibronectin that retain attachment-promoting activity. Peptides having a tetrapeptide recognition site are described in U.S. Pat. Nos. 4,589,881 and 4,614,517. A number of large polypeptide fragments in the cell-binding domain of fibronectin have cell-attachment activity. For example, see U.S. Pat. Nos. 4,517,686, 4,661,111 and U.S. Pat. No. 4,578,079.

Ruggeri et al., Proc. Nat'l Acad. Sci. U.S.A., 83, 5708-5712 (1986) explore a series of synthetic peptides designed in lengths to 16 residues, that contain RGD and a valine attached to the aspartic acid residue of RGD that inhibit fibrinogen binding to platelets. See also Koczewiak et al., Biochem. 23, 1767-1774 (1984); Ginsberg et al., J.
30 Biol. Chem. 260(7), 3931-3936 (1985); and Haverstick et al., Blood 66(4), 946-952 (1985). Other inhibitors are disclosed in Eur. Pat. App. Nos. 275,748 and 298,820.

A number of low molecular weight polypeptide factors have been isolated from snake venom. These factors apparently have high

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affinity for the gp IIb/IIIa complex. For example, Huang *et al.*, J. Biol Chem., 262, 16157-16163 (1987); Huang *et al.*, Biochemistry 28, 661-666 (1989) describe the primary structure of the venom trigramin which is a 72 amino acid polypeptide that contains the RGD subunit. Echistatin
5 is another compound which has high affinity for the gp IIb/IIIa complex. This polypeptide contains 49 amino acids and has the RGD subunit and various disulfide bridges. Gan *et al.*, J. Biol. Chem., 263, 19827-19832 (1988). See also, Dennis *et al.*, Proc. Nat'l Acad. Sci. USA, 87, 2471-2475 (1989). However, these snake venom factors also have high affinity
10 for other members of the adhesive protein receptor family including the vitronectin and fibronectin receptors so are not selective for the gp IIb/IIIa complex.

While it is known that the tripeptide sequence Arg-Gly-Asp is present in certain polypeptides that can duplicate or inhibit the cell
15 attachment-promoting effects of fibronectin and vitronectin, the tripeptide Arg-Gly-Asp has low activity. At present, there is little understanding of how other amino acids coupled to this sequence influence binding specificity. U.S. Pat. No 5,023,233, assigned to Merck & Co., Inc., discloses small cyclic hexapeptides which contain the sequence Arg-Gly-
20 Asp and are useful platelet aggregation inhibitors. U.S. Pat. No. 5,037,808 discloses the use of indolyl platelet-aggregation inhibitors which are believed to act by antagonizing interactions between fibrinogen and/or extracellular matrix proteins and the platelet gp IIb/IIIa receptor. U.S. Pat. No. 5,037,808 discloses guanidino peptide mimetic compounds
25 that retain an Asp residue which inhibit platelet aggregation. The application PCT/US90/02746 describes the use of antibody-poly-peptide conjugates wherein said polypeptides contain the Arg-Gly-Asp (RGD) sequence.

The application PCT/US91/00564 discloses the use of large
30 cyclic peptides containing RGD flanked by proline residues which are platelet aggregation inhibitors. The application PCT/US90/03788 discloses small cyclic platelet aggregation inhibitors which are synthetic cyclic pentapeptides containing the tripeptide sequence Arg-Gly-Asp and a thioether linkage in the cycle. The application PCT/US90/05367

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published May 2, 1991 also discloses the use of peptides and pseudopeptides such as N-amidino-piperidine-3-carboxylglycyl-L-aspartyl-L-valine that inhibit platelet aggregation and thrombus formation in mammalian blood. The application Eur. Pat. App. No. 91103462.7

5 discloses linear compounds which can include internal piperazinyl or piperidinyl derivatives. Eur. Pat. App. No. 91300179.8, assigned to Merck & Co., Inc., and published on July 17, 1991 discloses linear polypeptide fibrinogen receptor antagonists. Eur. Pat. App. No. 90101404.3 discloses compounds of the $R^1-A-(W)_a-X-(CH_2)_b-(Y)_c-B-Z-COOR$ wherein R^1 is a guandinino or amidino moiety and A and B are chosen from specific monosubstituted aryl or heterocyclic moieties.

10

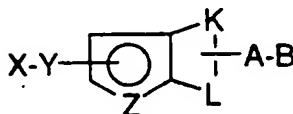
While a multitude of compounds or peptide analogs believed to inhibit platelet aggregation by inhibiting binding to a blood platelet by fibrinogen are known, the present invention provides novel fibrinogen

15 receptor antagonists that have significant binding activity and are, therefore, useful for the reasons stated herein. A number of very serious diseases and disorders involve hyperthrombotic complications which lead to intravascular thrombi and emboli. Myocardial infarction, stroke, phlebitis and a number of other serious conditions create the need for

20 novel and effective fibrinogen receptor antagonists.

SUMMARY OF THE INVENTION

A fibrinogen receptor antagonist of the following formula

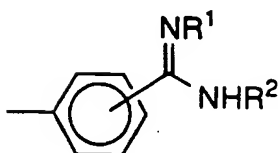
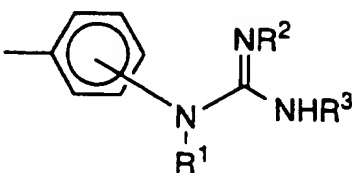
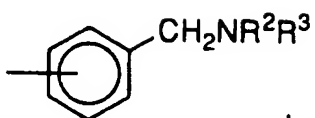
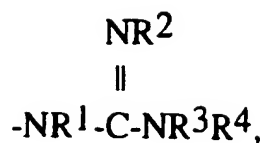


25 and pharmaceutically acceptable salts thereof, where

X is chosen from the group consisting of:



- 5 -



- 5 and a 5- to 6-membered mono- or bicyclic aromatic or nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O and S and either unsubstituted or substituted with R^1 , R^2 , R^3 or R^4 ,
 wherein R^1 , R^2 , R^3 and R^4 are independently selected from the group
 10 consisting of hydrogen,
 C_{1-10} alkyl,
 aryl C_{0-8} alkyl,
 oxo,
 thio,
 15 amino C_{0-8} alkyl, C_{1-3} acylamino C_{0-8} alkyl,
 C_{1-6} alkylamino C_{0-8} alkyl,
 C_{1-6} dialkylamino C_{0-8} alkyl,
 C_{1-4} alkoxy C_{0-6} alkyl,
 carboxy C_{0-6} alkyl,
 20 C_{1-3} alkoxy carbonyl C_{0-6} alkyl,
 C_{1-4} alkylthio C_{0-6} alkyl,

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aryl C₀₋₄ thio C₀₋₆ alkyl,
 carboxy C₀₋₆ alkyloxy, and
 hydroxy C₀₋₆ alkyl;

5 Z is chosen from the group consisting of:

-CR¹=CR²-,
 -CR¹=N-,
 -N=CR¹-, and
 S, O, and NR¹;

10

Y and A are independently chosen from the group consisting of

15
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-(CH}_2\text{)}_m\text{-, -(CH}_2\text{)}_m\text{CNR}^3\text{(CH}_2\text{)}_n\text{-, -(CH}_2\text{)}_m\text{NR}^3\text{C(CH}_2\text{)}_n\text{-,} \\ \text{-(CH}_2\text{)}_m\text{O(CH}_2\text{)}_n\text{-,} \end{array}$$

20
$$\begin{array}{c} \text{O} \qquad \qquad \text{S} \\ \parallel \qquad \qquad \parallel \\ \text{-(CH}_2\text{)}_m\text{C(CH}_2\text{)}_n\text{-, -(CH}_2\text{)}_m\text{C(CH}_2\text{)}_n\text{-, -(CH}_2\text{)}_m\text{SO}_2\text{(CH}_2\text{)}_n\text{-,} \\ \text{-(CH}_2\text{)}_m\text{S(CH}_2\text{)}_n\text{-, -(CH}_2\text{)}_m\text{SO(CH}_2\text{)}_n\text{-,} \\ \text{-(CH}_2\text{)}_m\text{SO}_2\text{NR}^3\text{(CH}_2\text{)}_n\text{-, -(CH}_2\text{)}_m\text{NR}^3\text{SO}_2\text{(CH}_2\text{)}_n\text{-,} \\ \text{-(CH}_2\text{)}_m\text{CR}^3\text{=CR}^4\text{(CH}_2\text{)}_n\text{-, -(CH}_2\text{)}_m\text{C=C(CH}_2\text{)}_n\text{-,} \\ \text{-(CH}_2\text{)}_m\text{CH(CH}_2\text{)}_n\text{-, and -(CH}_2\text{)}_m\text{aryl(CH}_2\text{)}_n\text{-,} \end{array}$$

25

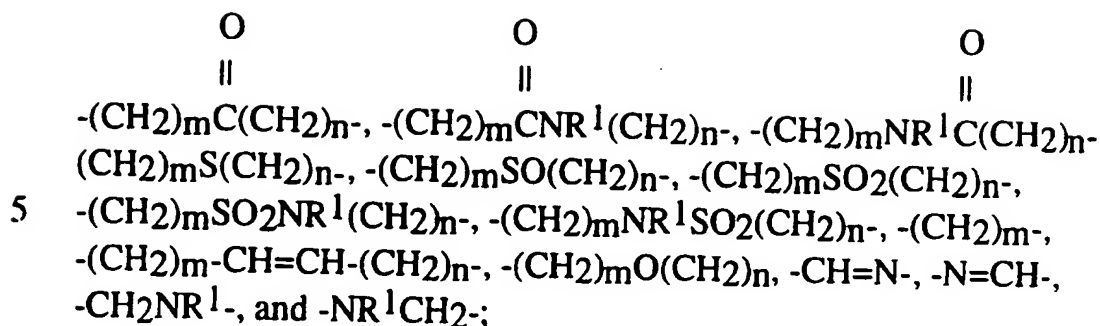
$$\begin{array}{c} \text{I} \\ \text{OH} \end{array}$$

- (CH₂)_mNR³(CH₂)_n-, and - (CH₂)_mNR³(CH₂)_n-,

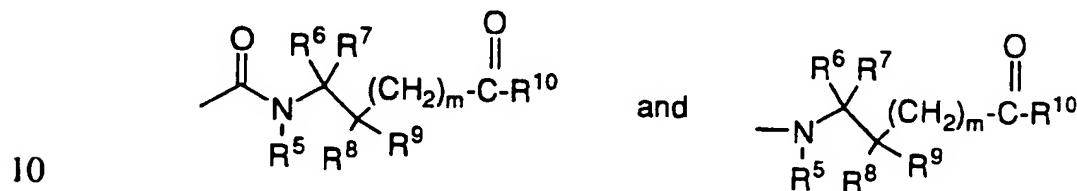
30 where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising K and L, and Y is attached to a ring atom of the ring comprising Z;

K and L are independently chosen from the group consisting of:

- 7 -



B is chosen from the group consisting of:



where $m = 0-2$, and

where $\text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8$ and R^9 are independently chosen from the group consisting of:

- hydrogen, fluorine, C_{1-8} alkyl, hydroxyl,
- $-\text{C}_{0-6}$ alkyl- $\text{CH}=\text{CH}-\text{C}_{0-6}$ alkyl,
- $-\text{C}_{0-6}$ alkyl- $\text{CH}=\text{CH}-\text{C}_{0-6}$ alkylaryl,
- $-\text{C}_{0-6}$ alkyl- $\text{C}\equiv\text{C}-\text{C}_{0-6}$ alkyl,
- $-\text{C}_{0-6}$ alkyl- $\text{C}\equiv\text{C}-\text{C}_{0-6}$ alkylaryl,
- hydroxy C_{1-6} alkyl, carboxy C_{0-6} alkyl,
- C_{1-6} alkyloxy, C_{3-8} cycloalkyl, aryl C_{1-6} alkyloxy,
- aryl C_{0-6} alkyl, C_{1-6} alkylcarbonyloxy,
- C_{0-6} alkylamino C_{0-6} alkyl,
- aryl C_{0-6} alkylamino C_{0-6} alkyl,
- C_{0-6} dialkylamino C_{0-6} alkyl,
- aryl C_{0-6} alkylcarbonyloxy,
- C_{1-8} alkylsulfonylamino C_{0-6} alkyl,
- C_{1-6} alkylaminocarbonyloxy,
- aryl C_{0-6} alkylaminocarbonyloxy,
- aryl C_{0-8} alkylsulfonylamino C_{0-6} alkyl,
- C_{1-8} alkyloxycarbonylamino C_{0-8} alkyl,

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- aryl C0-8 alkyloxycarbonylamino C0-8 alkyl,
 C1-8 alkylcarbonylamino C0-6 alkyl,
 aryl C0-6 alkylcarbonylamino C0-6 alkyl,
 C0-8 alkylaminocarbonylamino C0-6 alkyl,
 5 aryl C0-8 alkylaminocarbonylamino C0-6 alkyl,
 C0-8 alkylaminosulfonylamino C0-6 alkyl,
 aryl C0-8 alkylaminosulfonylamino C0-6 alkyl,
 C1-6 alkylsulfonyl C0-6 alkyl,
 aryl C0-6 alkylsulfonyl C0-6 alkyl,
 10 C1-6 alkylcarbonyl C0-6 alkyl,
 aryl C0-6 alkylcarbonyl C0-6 alkyl,
 C1-6 alkylthiocarbonylamino C0-6 alkyl,
 aryl C0-6 alkylthiocarbonylamino C0-6 alkyl,
 C0-8 alkylaminocarbonyl C0-6 alkyl, and
 15 aryl C0-8 alkylaminocarbonyl C0-6 alkyl,

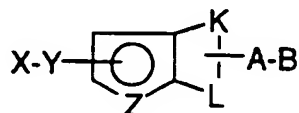
unsubstituted or substituted with one or more substituents selected from R¹ and R², and

- 20 $\begin{array}{c} \text{O} \\ \parallel \end{array}$
 C-AA, where AA is an L- or D-amino acid, or its corresponding ester, connected through an amide linkage;
- 25 R¹⁰ is chosen from the group consisting of:
 hydroxy,
 C1-8 alkyloxy,
 aryl C0-6 alkyloxy,
 C1-8 alkylcarbonyloxy C1-4 alkyloxy,
 30 aryl C1-8 alkylcarbonyloxy C1-4 alkyloxy,
 C1-8 alkylaminocarbonyl C1-4 alkyloxy,
 C1-8 dialkylaminocarbonyl C1-4 alkyloxy, and
 an L- or D- amino acid joined by an amide linkage, wherein the
 carboxylic acid moiety of said amino acid is as the free acid or is
 35 esterified by C1-6 alkyl.

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DETAILED DESCRIPTION OF THE INVENTION

A fibrinogen receptor antagonist of the following formula

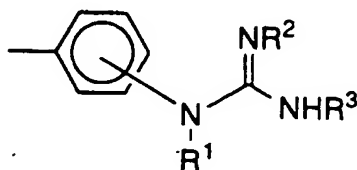
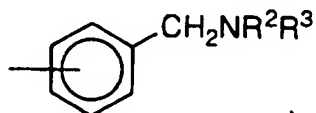
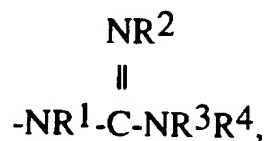
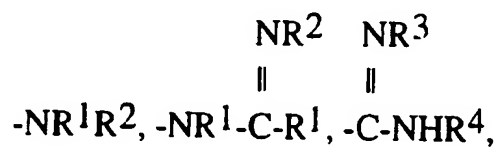


and pharmaceutically acceptable salts thereof, where

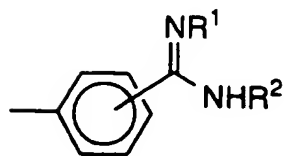
5

X is chosen from the group consisting of:

10



15



and a 5- to 6-membered mono- or bicyclic aromatic or nonaromatic ring system containing 0, 1, or 2 heteroatoms

- 10 -

selected from N, O and S and either unsubstituted or substituted with R¹, R², R³ or R⁴,
 wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen,

- 5 C₁-10 alkyl,
 aryl C₀-8 alkyl,
 oxo,
 thio,
 amino C₀-8 alkyl, C₁-3 acylamino C₀-8 alkyl,
 10 C₁-6 alkylamino C₀-8 alkyl,
 C₁-6 dialkylamino C₀-8 alkyl,
 C₁-4 alkoxy C₀-6 alkyl,
 carboxy C₀-6 alkyl,
 C₁-3 alkoxycarbonyl C₀-6 alkyl,
 15 C₁-4 alkylthio C₀-6 alkyl,
 aryl C₀-4 thio C₀-6 alkyl,
 carboxy C₀-6 alkyloxy, and
 hydroxy C₀-6 alkyl;

20 Z is chosen from the group consisting of:

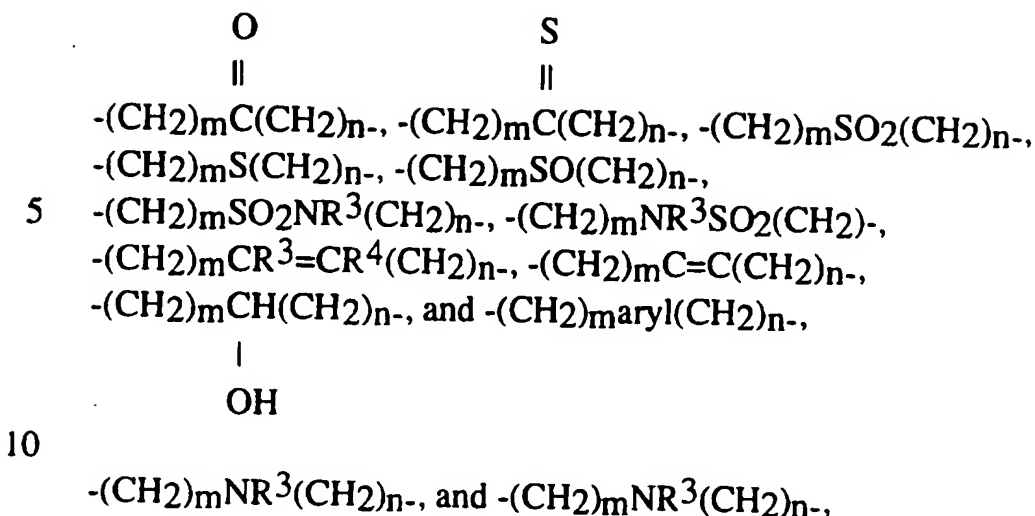
- CR¹=CR²-,
 -CR¹=N-,
 -N=CR¹-, and
 S, O, and NR¹;

25

Y and A are independently chosen from the group consisting of

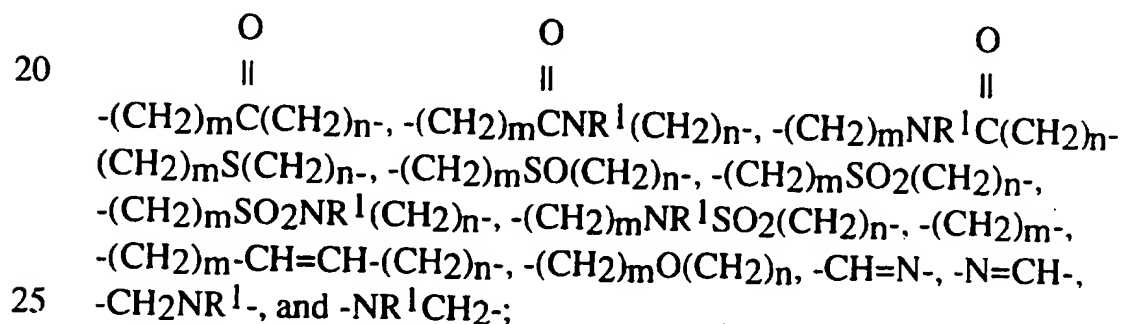
- 30
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-(CH}_2\text{)}_m\text{-} \end{array}$$
,
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-(CH}_2\text{)}_m\text{CNR}^3\text{(CH}_2\text{)}_n\text{-} \end{array}$$
,
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-(CH}_2\text{)}_m\text{NR}^3\text{C(CH}_2\text{)}_n\text{-} \end{array}$$
,
 -(CH₂)_mO(CH₂)_n-,

- 11 -

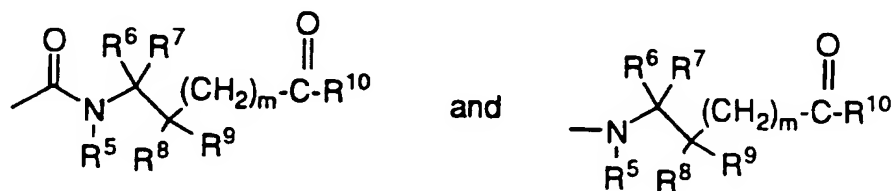


where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising K and L, and Y is attached to a ring atom of the ring comprising Z;

K and L are independently chosen from the group consisting of:



B is chosen from the group consisting of:



where m = 0-2, and

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where R5, R6, R7, R8 and R9 are independently chosen from the group consisting of:

- hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl,
- C₀₋₆ alkyl-CH = CH-C₀₋₆ alkyl,
- 5 -C₀₋₆ alkyl-CH = CH-C₀₋₆ alkylaryl,
- C₀₋₆ alkyl-C \equiv C-C₀₋₆ alkyl,
- C₀₋₆ alkyl-C \equiv C-C₀₋₆ alkylaryl,
- hydroxy C₁₋₆ alkyl, carboxy C₀₋₆ alkyl,
- C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl, aryl C₁₋₆ alkyloxy,
- 10 aryl C₀₋₆ alkyl, C₁₋₆ alkylcarbonyloxy,
- C₀₋₆ alkylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylamino C₀₋₆ alkyl,
- C₀₋₆ dialkylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonyloxy,
- 15 C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
- C₁₋₆ alkylaminocarbonyloxy,
- aryl C₀₋₆ alkylaminocarbonyloxy,
- aryl C₀₋₈ alkylsulfonylamino C₀₋₆ alkyl,
- C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
- 20 aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
- C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- 25 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
- aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
- C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
- 30 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
- C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylthiocarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminocarbonyl C₀₋₆ alkyl, and
- aryl C₀₋₈ alkylaminocarbonyl C₀₋₆ alkyl,

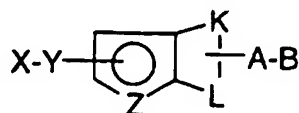
- 13 -

unsubstituted or substituted with one or more substituents selected from R¹ and R², and

5 $\begin{array}{c} \text{O} \\ \parallel \\ \text{C-AA, where AA is an L- or D-amino acid, or its corresponding ester, connected through an amide linkage;} \end{array}$

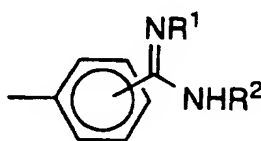
R¹⁰ is chosen from the group consisting of:
 10 hydroxy,
 C₁₋₈ alkyloxy,
 aryl C₀₋₆ alkyloxy,
 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
 aryl C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
 15 C₁₋₈ alkylaminocarbonyl C₁₋₄ alkyloxy,
 C₁₋₈ dialkylaminocarbonyl C₁₋₄ alkyloxy, and
 an L- or D- amino acid joined by an amide linkage, wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C₁₋₆ alkyl.

20 In one embodiment, compounds of the invention have the formula

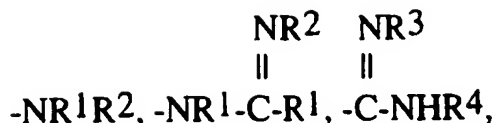


25 and pharmaceutically acceptable salts thereof, where

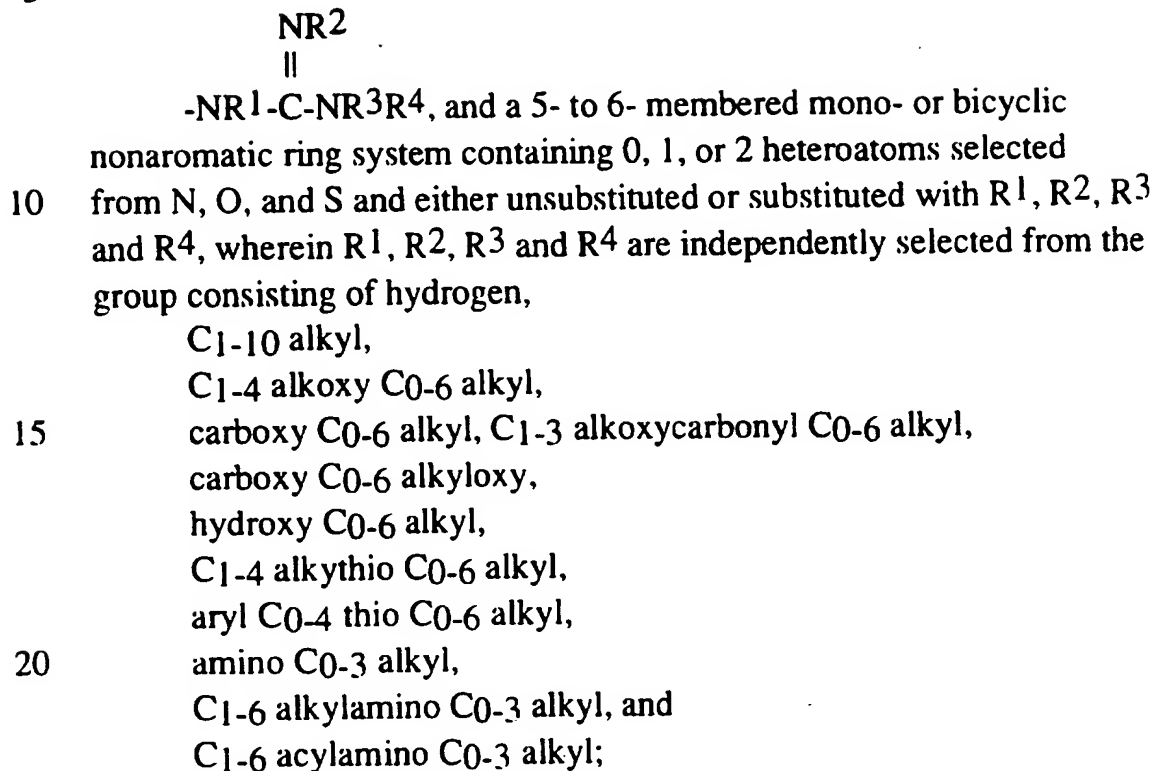
X is chosen from the group consisting of:



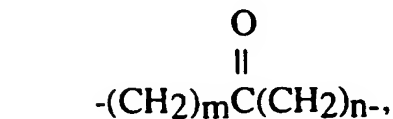
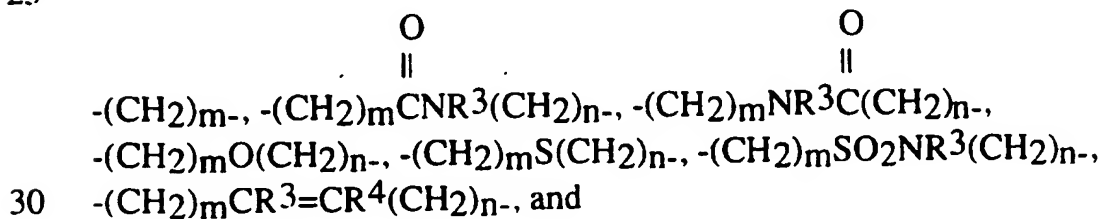
- 14 -



5



Y and A are independently chosen from the group consisting of:

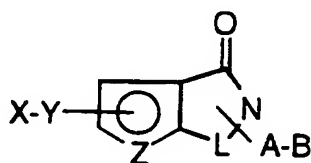


35

- 15 -

where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising K and L, and Y is attached to a ring atom of the ring comprising Z.

- 5 In a class of the embodiment, compounds of the invention have the formula



and pharmaceutically acceptable salts thereof, where

- 10 Z is chosen from the group consisting of:

-CR¹=CR²-, -C=NR¹-, -N=CR¹-, and S

- 15 Y and A are independently chosen from the group consisting of:

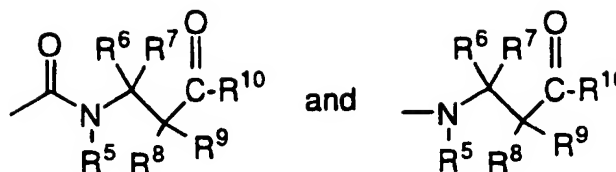
$$-(\text{CH}_2)_m-, -(\text{CH}_2)_m\overset{\text{O}}{\parallel}\text{CNR}^3(\text{CH}_2)_n-, -(\text{CH}_2)_m\overset{\text{O}}{\parallel}\text{NR}^3\text{C}(\text{CH}_2)_n-,$$

- 20
$$-(\text{CH}_2)_m\overset{\text{O}}{\parallel}\text{C}(\text{CH}_2)_n-, -(\text{CH}_2)_m\text{O}(\text{CH}_2)_n-, -(\text{CH}_2)_m\text{SO}_2(\text{CH}_2)_n-, \text{ and } -(\text{CH}_2)_m\text{SO}_2\text{NR}^3(\text{CH}_2)_n-,$$

- 25 where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising L, and Y is attached to a ring atom of the ring comprising Z;

- 30 B is chosen from the group consisting of:

- 16 -



where R⁵, R⁶, R⁷, R⁸ and R⁹ are independently chosen from:

hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl,

hydroxy C₁₋₆ alkyl,

5 -C₀₋₆ alkyl -CH = CH-C₀₋₆ alkyl,

-C₀₋₆ alkyl -CH = CH-C₀₋₆ alkylaryl,

-C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkyl,

-C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkylaryl,

carboxy C₀₋₆ alkyl, C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl,

10 aryl C₀₋₆ alkyl,

C₁₋₆ alkylcarbonyloxy, C₀₋₆ alkylamino C₀₋₆ alkyl,

aryl C₀₋₆ alkylcarbonyloxy,

C₀₋₆ dialkylamino C₀₋₆ alkyl,

C₁₋₆ alkylaminocarbonyloxy,

15 aryl C₁₋₆ alkylaminocarbonyloxy,

C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,

aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,

C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,

C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,

20 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,

C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,

aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,

C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,

aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,

25 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,

aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,

C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,

aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,

C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl; and

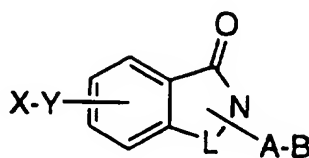
30

R¹⁰ is chosen from the group consisting of:

- 17 -

hydroxy,
C₁₋₈ alkyloxy, and
aryl C₀₋₆ alkyloxy.

- 5 In a subclass of the class of the embodiment, compounds have the formula

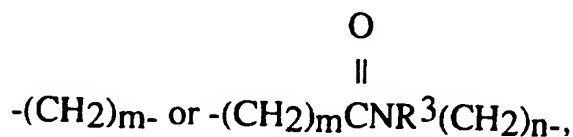


and pharmaceutically acceptable salts thereof, where

- 10 L is chosen from the group consisting of:

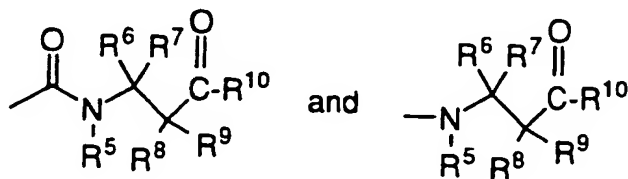
-CH₂- or -(CH₂)₂-;

- 15 Y and A are independently chosen from the group consisting of:



- 20 where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising L;

B is chosen from the group consisting of:



25

where R⁵, R⁶, R⁷, R⁸ and R⁹ are independently chosen from:
hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl,

- 18 -

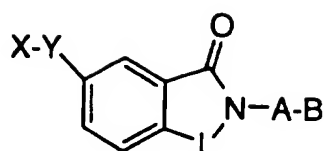
- hydroxy C₁₋₆ alkyl,
 -C₀₋₆ alkyl -CH = CH-C₀₋₆ alkyl,
 -C₀₋₆ alkyl -CH = CH-C₀₋₆ alkylaryl,
 -C₀₋₆ alkyl -C \equiv C-C₀₋₆ alkyl,
 5 -C₀₋₆ alkyl -C \equiv C-C₀₋₆ alkylaryl,
 carboxy C₀₋₆ alkyl, C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl,
 aryl C₀₋₆ alkyl,
 C₁₋₆ alkylcarbonyloxy, C₀₋₆ alkylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonyloxy,
 10 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 C₁₋₆ alkylaminocarbonyloxy,
 aryl C₁₋₆ alkylaminocarbonyloxy,
 C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
 15 C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
 C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 20 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
 C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
 25 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl; and

R¹⁰ is chosen from the group consisting of:

- hydroxy,
 30 C₁₋₈ alkyloxy, and
 aryl C₀₋₆ alkyloxy.

In a group of the subclass, compounds have the formula

- 19 -



and pharmaceutically acceptable salts thereof, where

5 X is a 6-membered monocyclic nonaromatic ring containing 0, 1 or 2 N heteroatoms either unsubstituted or substituted with R¹, R², R³ or R⁴, wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen,

10 C₁-10 alkyl,
C₁-4 alkoxy C₀-6 alkyl,
carboxy C₀-6 alkyl, C₁-3 alkoxycarbonyl C₀-6 alkyl,
carboxy C₀-6 alkyloxy
hydroxy C₀-6 alkyl
C₁-4 alkythio C₀-6 alkyl,
15 aryl C₀-4 thio C₀-6 alkyl,
amino C₀-3 alkyl,
C₁-6 alkylamino C₀-3 alkyl, and
C₁-6 acylamino C₀-3 alkyl;

20 L is chosen from the group consisting of:

-CH₂- or -(CH₂)₂;

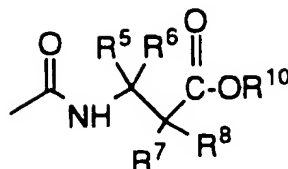
Y and A are independently chosen from the group consisting of:

25
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{-(CH}_2\text{)}_m\text{- or -(CH}_2\text{)}_m\text{CNR}^3\text{(CH}_2\text{)}_n\text{-,} \end{array}$$

30 where m and n are integers independently chosen from 0-6;

B is chosen from the group consisting of:

- 20 -



where R⁵, R⁶, R⁷, R⁸ and R⁹ are independently chosen from:
hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl,
hydroxy C₁₋₆ alkyl,

- 5 -C₀₋₆ alkyl -CH = CH-C₀₋₆ alkyl,
- C₀₋₆ alkyl -CH = CH-C₀₋₆ alkylaryl,
- C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkyl,
- C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkylaryl,
- carboxy C₀₋₆ alkyl, C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl,
- 10 aryl C₀₋₆ alkyl,
- C₁₋₆ alkylcarbonyloxy, C₀₋₆ alkylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonyloxy,
- C₀₋₆ dialkylamino C₀₋₆ alkyl,
- C₁₋₆ alkylaminocarbonyloxy,
- 15 aryl C₁₋₆ alkylaminocarbonyloxy,
- C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
- C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
- C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
- 20 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- 25 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
- aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
- C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
- C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl; and

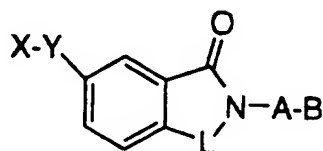
30

R¹⁰ is chosen from the group consisting of:

- 21 -

hydroxy,
C₁₋₈ alkyloxy, and
aryl C₀₋₆ alkyloxy.

5 In a subgroup of the group, compounds have the formula



and pharmaceutically acceptable salts thereof, where

10 X is a 6-membered monocyclic nonaromatic ring containing 0, 1 or 2 N heteroatoms either unsubstituted or substituted with R¹, R², R³ or R⁴, wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen,

15 C₁₋₁₀ alkyl,
C₁₋₄ alkoxy C₀₋₆ alkyl,
carboxy C₀₋₆ alkyl, C₁₋₃ alkoxycarbonyl C₀₋₆ alkyl,
carboxy C₀₋₆ alkyloxy,
hydroxy C₀₋₆ alkyl,
C₁₋₄ alkythio C₀₋₆ alkyl,
aryl C₀₋₄ thio C₀₋₆ alkyl,
20 amino C₀₋₃ alkyl,
C₁₋₆ alkylamino C₀₋₃ alkyl, and
C₁₋₆ acylamino C₀₋₃ alkyl;

25 L is chosen from the group consisting of:

-CH₂- or -(CH₂)₂- ;

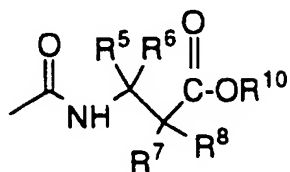
Y and A are independently chosen from the group consisting of:

30 -(CH₂)_m- ,

where m is an integer independently chosen from 0 and 1;

- 22 -

B is chosen from the group consisting of:



- where R⁵, R⁶, R⁷, R⁸, and R⁹ are independently chosen from:
- 5 hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl, hydroxy C₁₋₆ alkyl,
 - C₀₋₆ alkyl -CH = CH-C₀₋₆ alkyl,
 - C₀₋₆ alkyl -CH = CH-C₀₋₆ alkylaryl,
 - C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkyl,
 - 10 -C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkylaryl,
 - carboxy C₀₋₆ alkyl, C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl, aryl C₀₋₆ alkyl,
 - C₁₋₆ alkylcarbonyloxy, C₀₋₆ alkylamino C₀₋₆ alkyl, aryl C₀₋₆ alkylcarbonyloxy,
 - 15 C₀₋₆ dialkylamino C₀₋₆ alkyl, C₁₋₆ alkylaminocarbonyloxy, aryl C₁₋₆ alkylaminocarbonyloxy,
 - C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl, aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
 - 20 C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl, C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl, aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
 - C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl, aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 - 25 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl, aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 - C₁₋₆ alkylsulfonyl C₀₋₆ alkyl, aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
 - C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
 - 30 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,

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C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl; and

R¹⁰ is chosen from the group consisting of:

- 5 hydroxy,
 C₁₋₈ alkyloxy, and
 aryl C₀₋₆ alkyloxy.

10 The following compounds were tested and found to inhibit
platelet aggregation with IC₅₀ values between about 0.01 μM and 100
μM.

15 N-([7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(S)-(3-pyridyl)-β-alanine,

 N-([7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(R)-methyl-β-alanine,

20 N-([7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
β-alanine,

 N-([7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(R)-(2-phenethyl)-β-alanine,

25 N-([7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
2(S)-(phenylsulfonylamino)-β-alanine,

30 N-([7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
2(R)-(phenylsulfonylamino)-β-alanine,

 N-([6-(piperazin-1-yl)-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl)-3(R)-
methyl-β-alanine,

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- N-{{7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(R)-(2-chlorobenzyl)- β -alanine,
- 5 N-{{7-(4-benzylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(R)-(2-chlorobenzyl)- β -alanine,
- N-{{7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3-(3-fluorophenyl)- β -alanine,
- 10 N-{{7-(piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(R)-(ethynyl)- β -alanine,
- N-{{7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(S)-(3-pyridyl)- β -alanine ethyl ester,
- 15 N-{{6-(Piperazin-1-yl)-2,3-dihydro-1(1H)-isoindolone-2-yl}acetyl}-3(R)-methyl- β -alanine n-butyl ester,
- N-{{7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(R)-methyl- β -alanine ethyl ester,
- 20 N-{{7-(4-Benzylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(R)-2(2-chlorobenzyl)- β -alanine ethyl ester, and
- 25 N-{{7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(R)-(ethynyl)- β -alanine ethyl ester.

Platelet aggregation is measured at 37°C in a Chronolog aggregometer. The reaction mixture contains gel-filtered human platelets

30 (2 x 10⁸ per ml), fibrinogen (100 micrograms per ml (ug/ml)), Ca²⁺ (1mM), and the compound to be tested. The aggregation is initiated by adding 10mM ADP 1 minute after the other components are added. The reaction is then allowed to proceed for at least 2 minutes. The extent of inhibition of aggregation is expressed as the percentage of the rate of

- 25 -

aggregation observed in the absence of inhibitor. The IC₅₀ is the dose of a particular compound inhibiting aggregation by 50% relative to a control lacking the compound.

5 The novel compounds of the present invention were prepared according to the procedure of the following examples. The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties
10 may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celcius
15 unless otherwise noted.

In addition to the following preparative procedures, several examples of in-vitro bioactivity of compounds within the scope of the present invention are indicated. To illustrate, one test which is used to evaluate fibrinogen receptor antagonist activity is based on evaluation of
20 inhibition of ADP-stimulated platelets. Aggregation requires that fibrinogen bind to and occupy the platelet fibrinogen receptor site. Inhibitors of fibrinogen binding inhibit aggregation. In the ADP-stimulated platelet aggregation assay used to determine inhibition associated with the compounds claimed in the instant invention, human
25 platelets are isolated from fresh blood, collected into acid citrate/dextrose by differential centrifugation followed by gel filtration on Sepharose 2B in divalent ion-free Tyrode's buffer (pH 7.4) containing 2% bovine serum albumin.

30 The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts:
acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride,

- 26 -

clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

10 The compounds of the present invention may be chiral; included within the scope of the present invention are racemic mixtures and separated enantiomers of formula (I). Furthermore all diastereomers, including E, Z isomers, of formula (I) are included in the present scope. Furthermore, hydrates as well as anhydrous compositions and polymorphs of formula (I) are within the present invention.

15 Prodrugs, such as ester derivatives of described compounds, are compound derivatives which, when absorbed into the bloodstream of a warm-blooded animal, cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

20 The term "pharmaceutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician. The term "anti-coagulant" shall include heparin, and warfarin. The term "thrombolytic agent" shall include agents such as streptokinase and tissue plasminogen activator. The term "platelet anti-aggregation agent" shall include agents such as aspirin and dipyridamole.

 The term "alkyl" means straight or branched alkane, alkene or alkyne.

30 The term "aryl" means a 5- or 6-membered aromatic ring containing 0, 1, or 2 heteroatoms selected from O, N, and S.

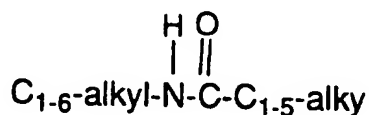
 The terms "alkyloxy" or "alkoxy" include an alkyl portion where alkyl is as defined above.

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The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. The C_{0-n} or C_{1-n} designation where n may be an integer from 1-10 or 2-10 respectively refers to the alkyl component of the arylalkyl or alkylaryl unit.

The term "halogen" includes fluorine, chlorine, iodine and bromine.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. For example, a C₁₋₆ alkyl substituted with C₁₋₅ alkylcarbonylamino is equivalent to



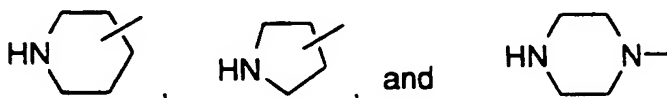
Amino acids suitable for compounds of the present invention include naturally occurring L- or D-amino acids include, for example, those naturally occurring L-amino acids present in humans, e.g. protein amino acids, including L-alanine, L-arginine, L-asparagine, L-aspartic acid, L-cysteine, L-glutamine, L-glutamic acid, L-glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, and L-valine, and those naturally occurring D-amino acids which are non-protein amino acids, such as those found, for example, in antibiotic substances produced by bacteria and fungi, including D-valine, D-asparagine, D-glutamate, D-ornithine, D-phenylalanine, D-leucine, D-cysteine, and D-aspartate. (see Zubay "BIOCHEMISTRY" Addison-Wesley Publishing Company, Inc. (Reading, MA) 1983 pp. 867-870 and Stryer "BIOCHEMISTRY" W.H. Freeman and Company (New York, NY) 3rd Edition 1988 pp. 16-21).

In the schemes and examples below, various reagent symbols have the following meanings:

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	BOC(or Boc):	t-butyloxycarbonyl.
	Pd-C:	Palladium on activated carbon catalyst.
	DMF:	Dimethylformamide.
	DMSO:	Dimethylsulfoxide.
5	CBZ:	Carbobenzyloxy.
	CH ₂ Cl ₂ :	Methylene chloride.
	CHCl ₃ :	chloroform.
	EtOH:	ethanol.
	MeOH:	methanol.
10	NBS:	N-bromosuccinimide
	EtOAc:	ethyl acetate.
	HOAc:	acetic acid.
	EDC:	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.
15	NaHMDS	sodium bis(trimethylsilyl)amide.
	HOBT	1-Hydroxybenzotriazole hydrate.
	TFA	Trifluoroacetic acid.
	LDA:	Lithium diisopropylamide.

20 X, a terminal basic moiety of compound of the invention, is exemplified by heterocyclic rings such as



and heteroaromatic rings such as



25

as well as amino, amidino, and guanadino moieties.

The compounds of the present invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers,

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tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent.

Compounds of the invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of this invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between gp IIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the circuit. (Gluszko *et al.*, *Amer. J. Physiol.*, 252(H), 615-621 (1987)). Platelets released from artificial surfaces show impaired hemostatic function. Compounds of the invention may be administered to prevent adhesion.

Other applications of these compounds include prevention of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty or coronary artery bypass procedures. They may also be used to prevent myocardial infarction.

The invention also includes the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating

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thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.9 mg/day to 9 g/day, most preferably between 0.9 mg/day and 1.8 g/day. A composition containing the medicament will range from 0.225 mg to 4.5 g. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in divided doses of two, three, or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regime.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with convention pharmaceutical practices.

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For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid,

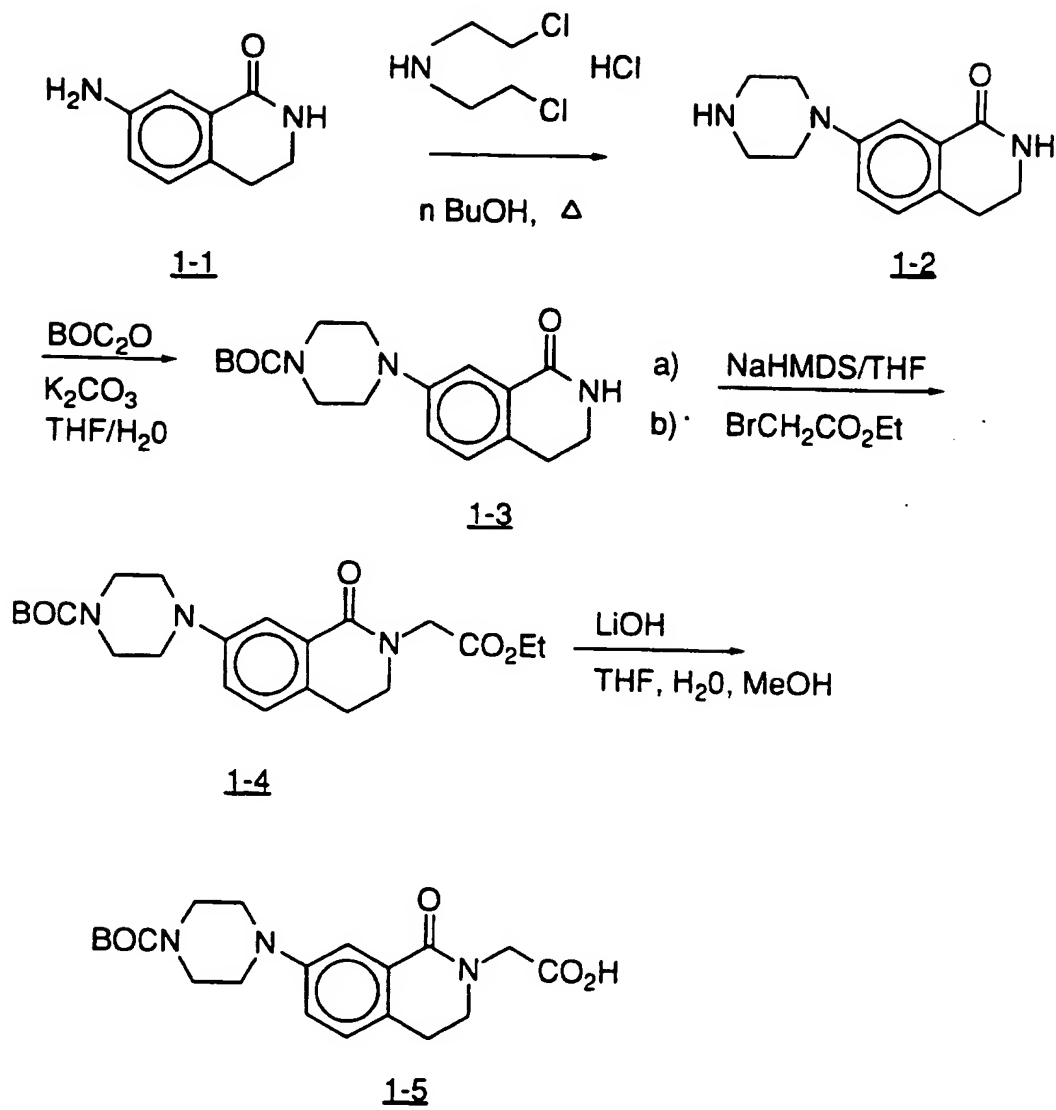
- 32 -

polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

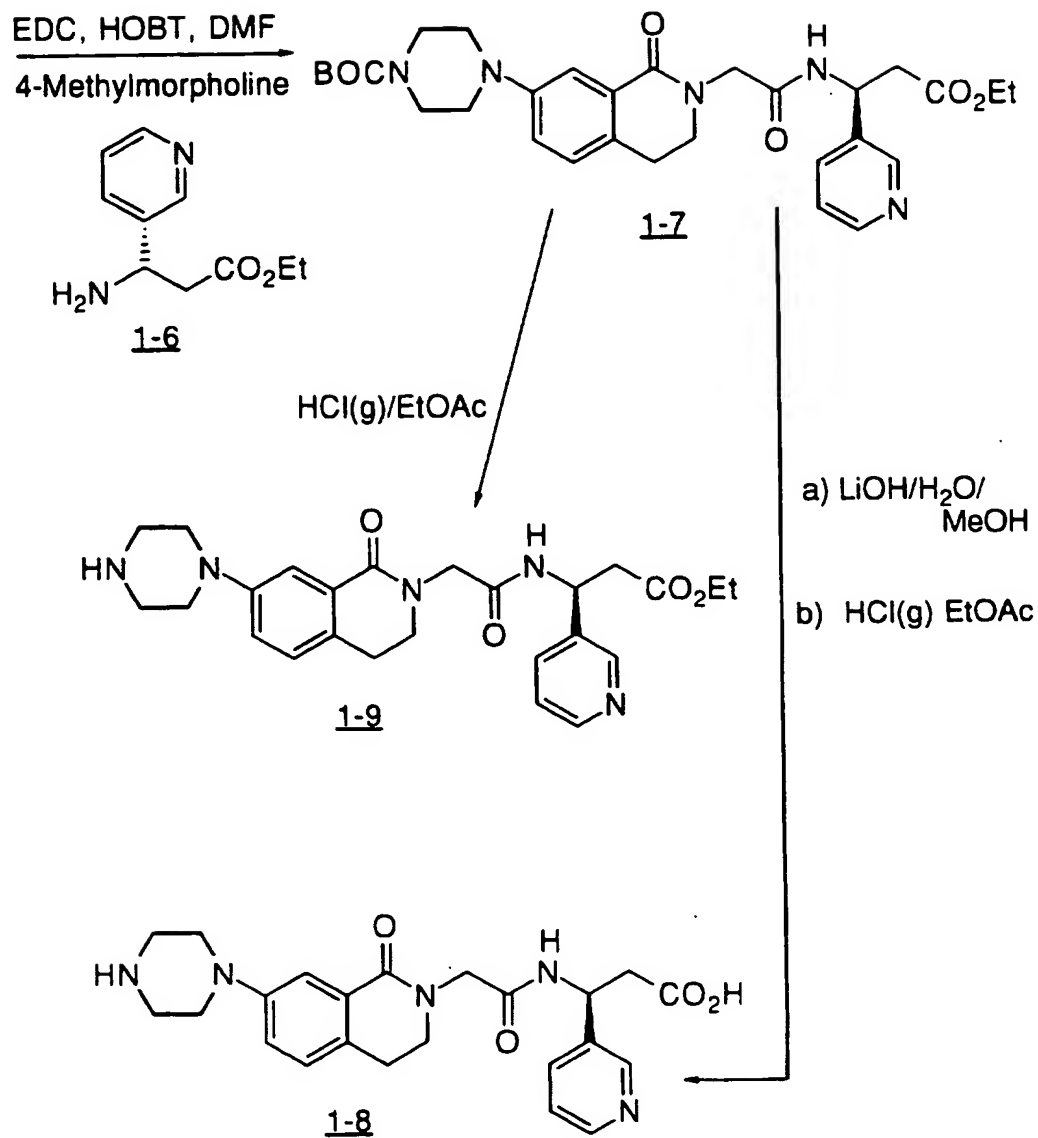
- 5 The compounds of the present invention can also be co-administered with suitable anticoagulation agents or thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies. They may also be combined with heparin, aspirin, or warfarin.

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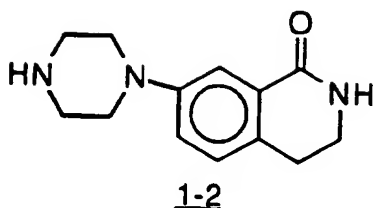
SCHEME I



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7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone (1-2)

5 A solution of 7-amino-3,4-dihydro-1(1H)-isoquinolinone (1-1) (Girard *et al*, *J. Org. Chem.*, 1983, vol. 48, p. 3220; 5.0 g, 30.8 mmol) and bis(2-chloroethyl)amine hydrochloride (6.3 g, 33.9 mmol) in n-butanol (250 mL) was stirred at 110°C for 3 days. The precipitate was removed by filtration to provide the starting amine as the HCl salt (3.6 g).
 10 Evaporation of the n-butanol under reduced pressure afforded a dark oil which was purified by column chromatography (silica gel; EtOH/H₂O/NH₄OH 10:0.5:0.5) to give 1-2. ¹H NMR (CD₃OD); δ 2.86 (2H, t), 3.10 (4H, m), 3.22 (4H, m), 3.44 (2H, t), 7.18 (2H, m), 7.55 (1H, m).

7-(4-t-Butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H) isoquinolinone (1-3)

7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone (1-2) (2.22 g, 9.61 mmol), Boc₂O (2.30 g, 10.6 mmol) and K₂CO₃ (1.33 g, 9.61 mmol) were stirred in THF (20 mL) and H₂O (20 mL) for 24 hours. The solution was poured into water and extracted with EtOAc (3x), washed with water then brine, dried (MgSO₄) and evaporated. Chromatography of the residue (EtOAc) gave a yellow solid which was swished with ether to afford 1-3 as a white solid. R_f (silica, EtOAc) =
 25 0.32.

Ethyl [7-(4-t-butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetate (1-4)

30 A solution of 7-(4-t-butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone (1-3) (2.37 g, 7.16 mmol) in THF (30 mL) at -78°C under argon was treated with NaHMDS (1M solution in THF;

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N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(S)-(3-pyridyl)- β -alanine (1-8)

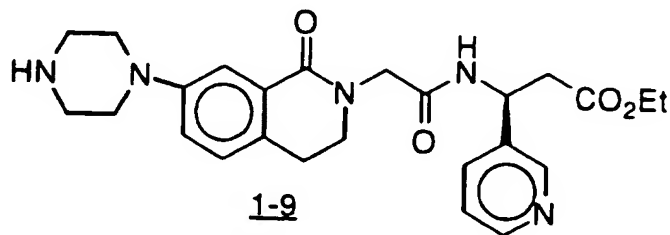
The ester 1-7 (77 mg, 0.14 mmol) was hydrolysed with 1N LiOH (0.41 mL, 0.41 mmol) and MeOH (2 mL) for 16 hours. The solvent was removed, the residue was suspended in EtOAc and H₂O and HCl gas was bubbled into the mixture. After 30 minutes, the solvent was removed in vacuo and the crude product was then purified by reverse phase HPLC (C18 column, H₂O/CH₃CN with 0.1% TFA, gradient) to give 1-8 as the TFA salt.

FAB mass spectrum m/z = 438 (M+1)

Anal. Calcd for C₂₃H₂₇N₅O₄•2.65 TFA • 2.0 H₂O

C, 43.82; H, 4.37; N, 9.03

found C, 43.84; H, 4.39; N, 9.18



N-([7-(4-t-Butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(S)-(3-pyridyl)- β -alanine ethyl ester (1-9)

1-7, (140 mg) was dissolved in 10 ml EtOAc and HCl gas bubbled through until the solution was saturated. After stirring for 1 hour, the solvent was removed and the residue purified by reverse phase HPLC (C18 column, H₂O/CH₃CN with 0.1% TFA, gradient) to give 1-9 as the TFA salt.

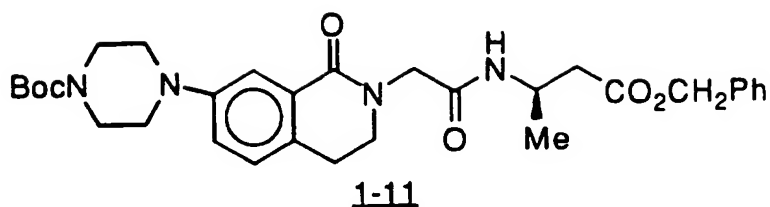
FAB mass spectrum m/z = 466 (M+1)

Anal. Calcd for C₂₅H₃₁N₅O₄•3.85 TFA • 2.0 H₂O

C, 41.75; H, 4.16; N, 7.45

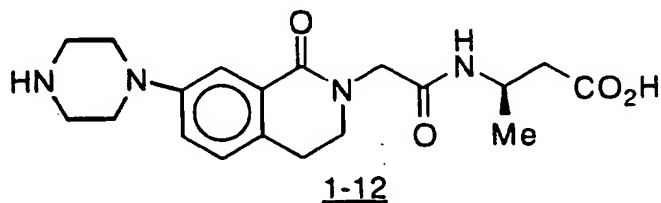
found C, 41.75; H, 4.00; N, 7.74

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N-([7-(4-t-Butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(H)-
isoquinolinone-2-yl]acetyl)-3(R)-methyl- β -alanine benzyl ester (1-11)

- 5 Following the procedure described for 1-7, but substituting
3(R)-methyl- β -alanine benzyl ester (1-10 Celgene) for ethyl 3-amino-
3(S)-(3-pyridyl) propionate dihydrochloride, 1-11 was prepared. ^1H
NMR (CDCl_3): δ 1.22 (3H, d), 1.49 (9H, s), 2.56 (2H, d), 2.95 (2H, m),
3.15 (4H, m), 3.57 (6H, m), 4.03 (1H, d, $J = 15$ Hz), 4.28 (1H, d, $J = 15$
10 Hz), 4.48 (1H, m), 5.04 (2H, s), 6.74 (1H, d), 7.07 (1H, dd), 7.13 (1H, d),
7.33 (5H, m), 7.62 (1H, d).



- 15 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(H)-isoquinolinone-2-yl]acetyl)-
3(R)-methyl- β -alanine (1-12)

Following the procedure described for 1-8, the ester 1-11
was converted into 1-12 as the TFA salt.

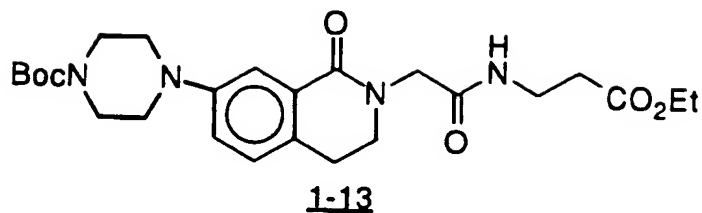
FAB mass spectrum $m/z = 375$ ($M+1$)

- 20 Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_4 \cdot 1.45 \text{ TFA} \cdot 1.7 \text{ H}_2\text{O}$

C, 46.11; H, 5.45; N, 9.82

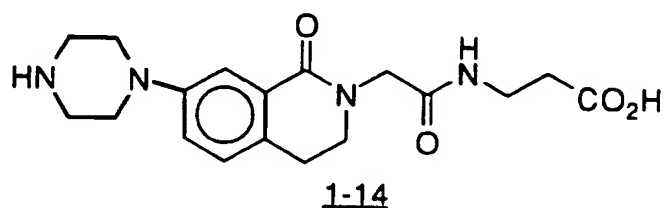
found C, 46.12; H, 5.42; N, 10.13

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N-([7-(4-t-Butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H)-
isoquinolinone-2-yl]acetyl)-β-alanine ethyl ester (1-13)

- 5 Following the procedure described for 1-7, but substituting β-alanine ethyl ester hydrochloride (Aldrich) for ethyl 3-amino-3(S)-(3-pyridyl)propionate dihydrochloride, the title compound was prepared. R_f (silica, EtOAc) = 0.3.



10

N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
β-alanine (1-14)

- 15 Following the procedure described for 1-8, the ester 1-12 was converted into 1-14 as the TFA salt.

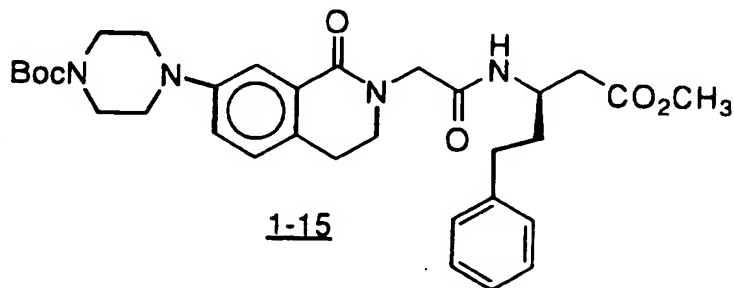
FAB mass spectrum m/z = 361 (M+1)

Anal. Calcd for $C_{18}H_{24}N_4O_4 \cdot 0.65 \text{ TFA} \cdot 0.9 \text{ H}_2\text{O}$

C, 45.30; H, 4.90; N, 9.92

found C, 45.29; H, 4.86; N, 10.24

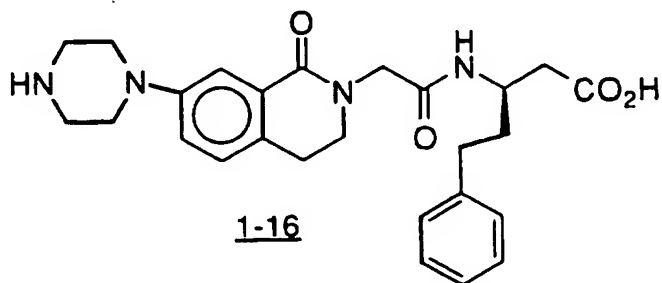
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N-{{7-(4-t-Butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(R)-(2-phenethyl)- β -alanine methyl ester (1-15)

- 5 Following the procedure described for 1-7, but substituting 3(R)-(2-phenethyl)- β -alanine methyl ester hydrochloride (1-15a) (US Patent 5,281,585) for ethyl 3-amino-3(S)-(3-pyridyl)propionate dihydrochloride, the title compound was prepared. R_f (silica, 10% MeOH in EtOAc) = 0.78.



10

N-{{7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-3(R)-(2-phenethyl)- β -alanine (1-16)

- 15 Following the procedure described for 1-8, the ester from 1-15 was converted into 1-16 as the TFA salt.

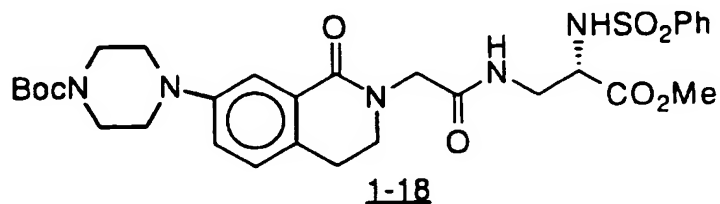
FAB mass spectrum m/z = 465 (M+1)

Anal. Calcd for $C_{26}H_{32}N_4O_4 \cdot 2.1 \text{ TFA} \cdot 1.0 \text{ H}_2\text{O}$

C, 50.23; H, 5.04; N, 7.76

found C, 50.12; H, 4.93; N, 7.91

20

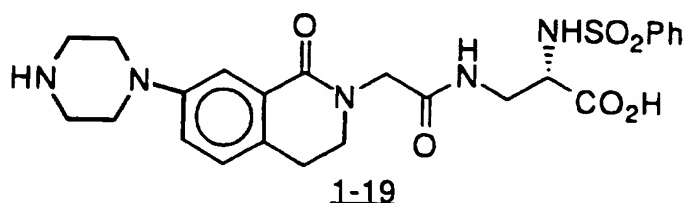


- 25 N-{{7-(4-t-Butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl}acetyl}-2(S)-(phenylsulfonylamino)- β -alanine methyl ester (1-18)

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Following the procedure described for 1-7, but substituting 2(S)-(phenylsulfonylamino)- β -alanine ethyl ester hydrochloride (1-17) (WO 94/12181) for ethyl 3-amino-3(S)-(3-pyridyl)propionate dihydrochloride, 1-18 was prepared. R_f (silica, EtOAc) = 0.37.

5



N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-2(S)-(phenylsulfonylamino)- β -alanine (1-19)

10

Following the procedure described for 1-8, the ester 1-18 was converted into 1-19 as the TFA salt.

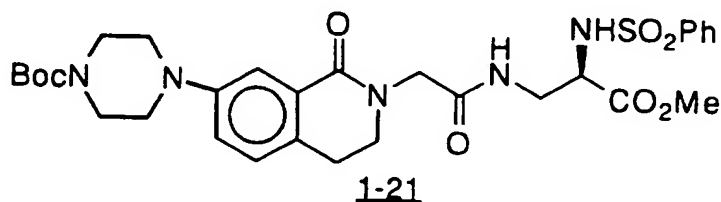
FAB mass spectrum m/z = 516 (M+1)

Anal. Calcd for $C_{24}H_{29}N_5O_6S \cdot 1.7 \text{ TFA} \cdot 1.0 \text{ H}_2\text{O}$

C, 45.24; H, 4.53; N, 9.63

15

found C, 45.22; H, 4.36; N, 9.94



N-([7-(4-t-Butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-2(R)-(phenylsulfonylamino)- β -alanine methyl ester (1-21)

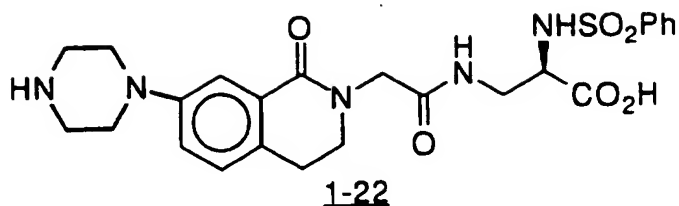
20

Following the procedure described for 1-7, but substituting 2(R)-(phenylsulfonylamino)- β -alanine for ethyl 3-amino-3(S)-(3-pyridyl)propionate dihydrochloride, the title compound was prepared.

25

^1H NMR (CD_3OD): δ 1.50 (9H, s), 3.00 (2H, m), 3.18 (2H, m), 3.3-3.7 (10H, m), 4.09 (1H, dd), 4.23 (2H, m), 7.2 (2H, m), 7.5-7.6 (4H, m), 7.85 (2H, m), 8.22 (1H, m).

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N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-2(R)-(phenylsulfonylamino)-β-alanine (1-22)

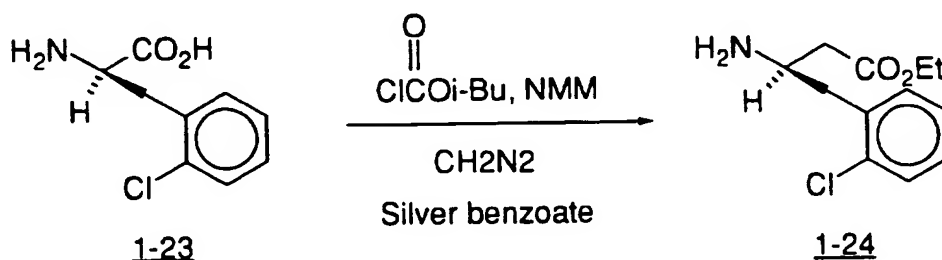
5 Following the procedure described for 1-8, the ester 1-21 was converted into 1-22 and was purified by reverse phase HPLC (C18 column, H₂O/CH₃CN with 0.1% TFA, gradient) to give the 1-22 as the TFA salt.

FAB mass spectrum $m/z = 516$ (M+1)

10 Anal. Calcd for $C_{24}H_{29}N_5O_6S \cdot 2.0 \text{ TFA} \cdot 1.75H_2O$

C, 43.39; H, 4.49; N, 9.03

found C, 43.36; H, 4.16; N, 9.26



15

3(R)-(2-Chlorobenzyl)-β-alanine ethyl ester hydrochloride (1-24)

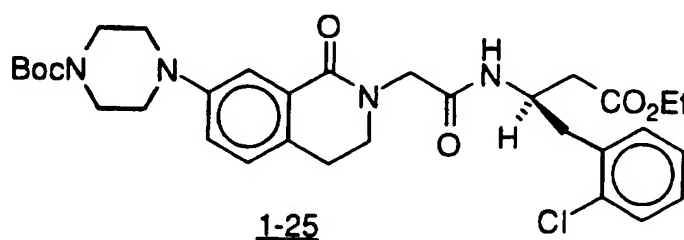
N-BOC-D-3-(2-chlorophenyl)alanine 1-23 (Synthetech, 3.0 g, 10 mmol) in EtOAc (80 mL) at 0°C was heated with N-methylmorpholine (1.32 mL, 12 mmol) and isobutylchloroformate (1.6 mL, 12 mmol) and stirred for 3 hours. The solution was poured into H₂O, extracted with EtOAc (x 2), washed with brine, dried (MgSO₄) and the solvent removed to give an oil. The oil was heated with excess ethereal diazomethane for 30 minutes, then the solution was purged with argon and evaporated to give a yellow oil.

25 To this yellow oil was added EtOH (80 mL), Et₃N (1.6 mL, 12 mmol) and then silver benzoate (700 mg, 4 mmol). After stirring for

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30 minutes the solution was concentrated and the crude product was purified by silica gel chromatography (eluting with 15% EtOAc in hexane) to give a white solid (1.1 g).

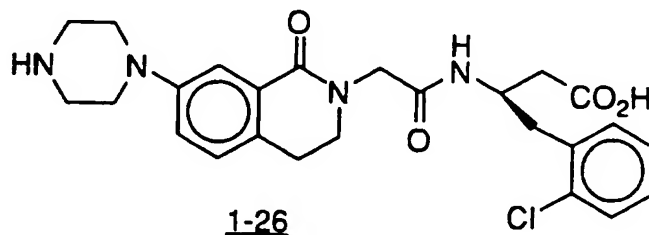
- 5 Deprotection of the resulting solid using HCl in EtOAc afforded 1-24 as a waxy solid (945 mg). R_f (silica; 10% MeOH in CH_2Cl_2) = 0.53.



- 10 N-([7-(4-*t*-Butoxycarbonyl piperazin-1-yl)-3,4-dihydro-1(*H*)-isoquinoline-2-yl]acetyl)-3(*R*)-(2-chlorobenzyl)- β -alanine ethyl ester (1-25)

- 15 Following the procedure described for 1-7 but using 3(*R*)-(2-chlorobenzyl)- β -alanine ethyl ester hydrochloride (1-24) as starting material, 1-25 was obtained as an oil.

^1H NMR (CDCl_3): δ 1.25 (3H, t), 1.50 (9H, s), 2.58 (2H, d), 2.8-3.1 (4H, m), 3.18 (4H, m), 3.3-3.5 (2H, m), 3.6 (4H, m), 4.00 (1H, d), 4.10 (2H, q), 4.21 (1H, d), 4.60 (1H, m), 6.9-7.2 (6H, m), 7.65 (1H, s).



20 N-([7-(Piperazin-1-yl)-3,4-dihydro 1(*H*)-isoquinoline-2-yl]acetyl)-3(*R*)-(2-chlorobenzyl)- β -alanine (1-26)

- 25 Following the procedure described for 1-8, 1-25 was converted into the title compound and isolated after reverse phase HPLC as the TFA salt.

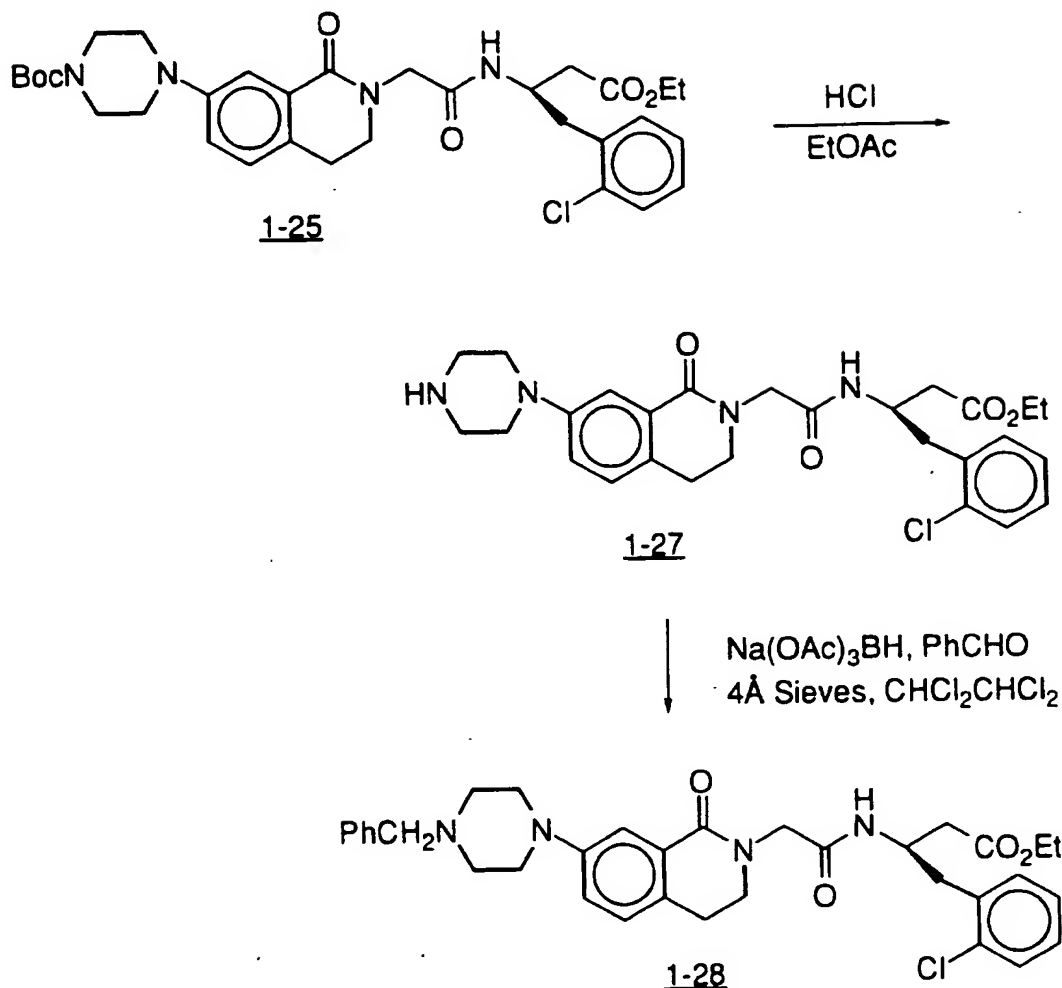
- 44 -

FAB mass spectrum $m/z = 485$ ($m + 1$)Anal. Calcd. for $C_{25}H_{29}N_4O_4Cl \cdot 1.9$ TFA

C, 49.30; H, 4.44; N, 7.99

found C, 49.03; H, 4.45; N, 8.34

5



N-([7-(4-Benzylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(R)-(2-chlorobenzyl)-β-alanine ethyl ester (1-28)

10

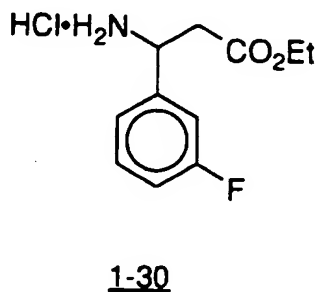
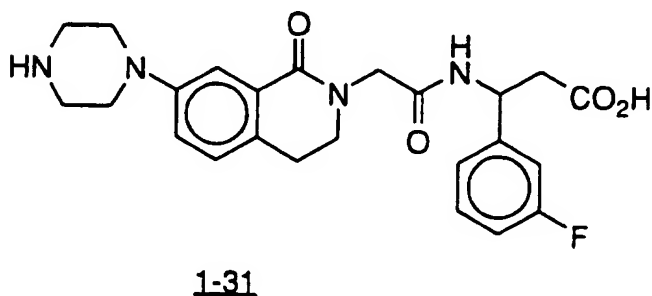
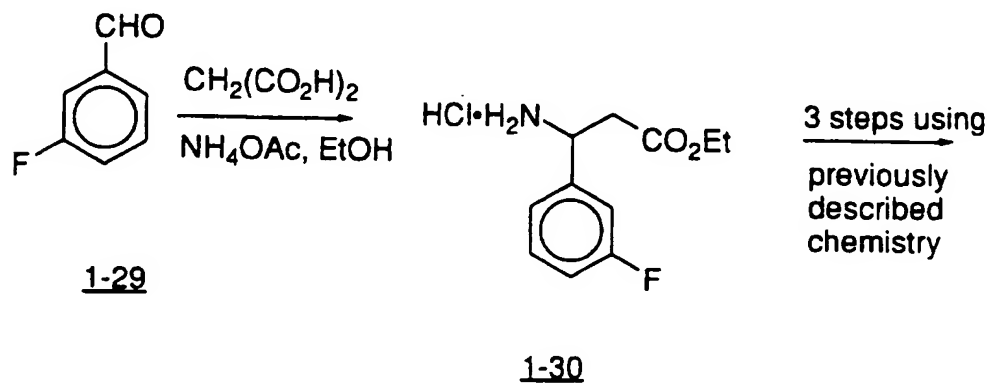
N-([7-(4-t-butoxycarbonylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(R)-(2-chlorobenzyl)-β-alanine ethyl ester (**1-25**) (212 mg, 0.35 mmol) was treated with $HCl/EtOAc$ to give the corresponding deprotected compound **1-27**.

- 45 -

To this compound (100 mg, 0.18 mmol) in 1,2-dichloroethane (4 mL) was added 4Å sieves, benzaldehyde (22.2 µL, 0.22 mmol), sodium triacetoxyborohydride (116 mg, 0.55 mmol) and Et₃N (25.4 µL, 0.18 mmol) and the mixture was stirred for 16 hours at room temperature.

- 5 After filtration through celite, the solution was poured into saturated NaHCO₃, extracted with EtOAc (x2), washed with brine, dried (MgSO₄) and the solvent removed in vacuo. Chromatography of the residue (silica; 5% MeOH in CHCl₃) afforded 1-28 as an oil. R_f (silica; 5% MeOH in CHCl₃) = 0.5.

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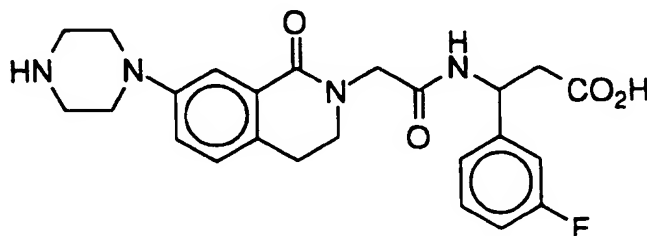


- 46 -

3-(3-Fluorophenyl)- β -alanine ethyl ester hydrochloride (1-30)

A solution of malonic acid (2.9 g, 27.8 mmol), 4-fluorobenzaldehyde 1-29 (2.6 mL, 24.2 mmol) and NH_4OAc (2.42 g, 31.4 mmol) in EtOH (80 mL) was heated at reflux for 16 hours. The mixture
5 was cooled and the precipitate was collected by filtration and washed with cold EtOH to give a white solid (1.9 g).

This solid (1.9 g) was dissolved in EtOH (100 mL) and HCl (g) was bubbled through the solution for 10 minutes. After stirring for 24 hours, the solvent was removed to provide 1-30. ^1H NMR (CD_3OD): δ
10 1.19 (3H, t), 2.99 (1H, dd), 3.08 (1H, dd), 4.17 (2H, q), 4.75 (1H, t) 7.15-7.35 (3H, m), 7.5 (1H, m).

1-31

15 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3-(3-fluorophenyl)- β -alanine (1-31)

Following the procedure of 1-7 and 1-8, but using 3-(3-fluorophenyl)- β -alanine ethyl ester hydrochloride 1-30 as starting material, 1-31 was obtained as the TFA salt.

20 FAB mass spectrum $m/z = 455$ ($m + 1$).

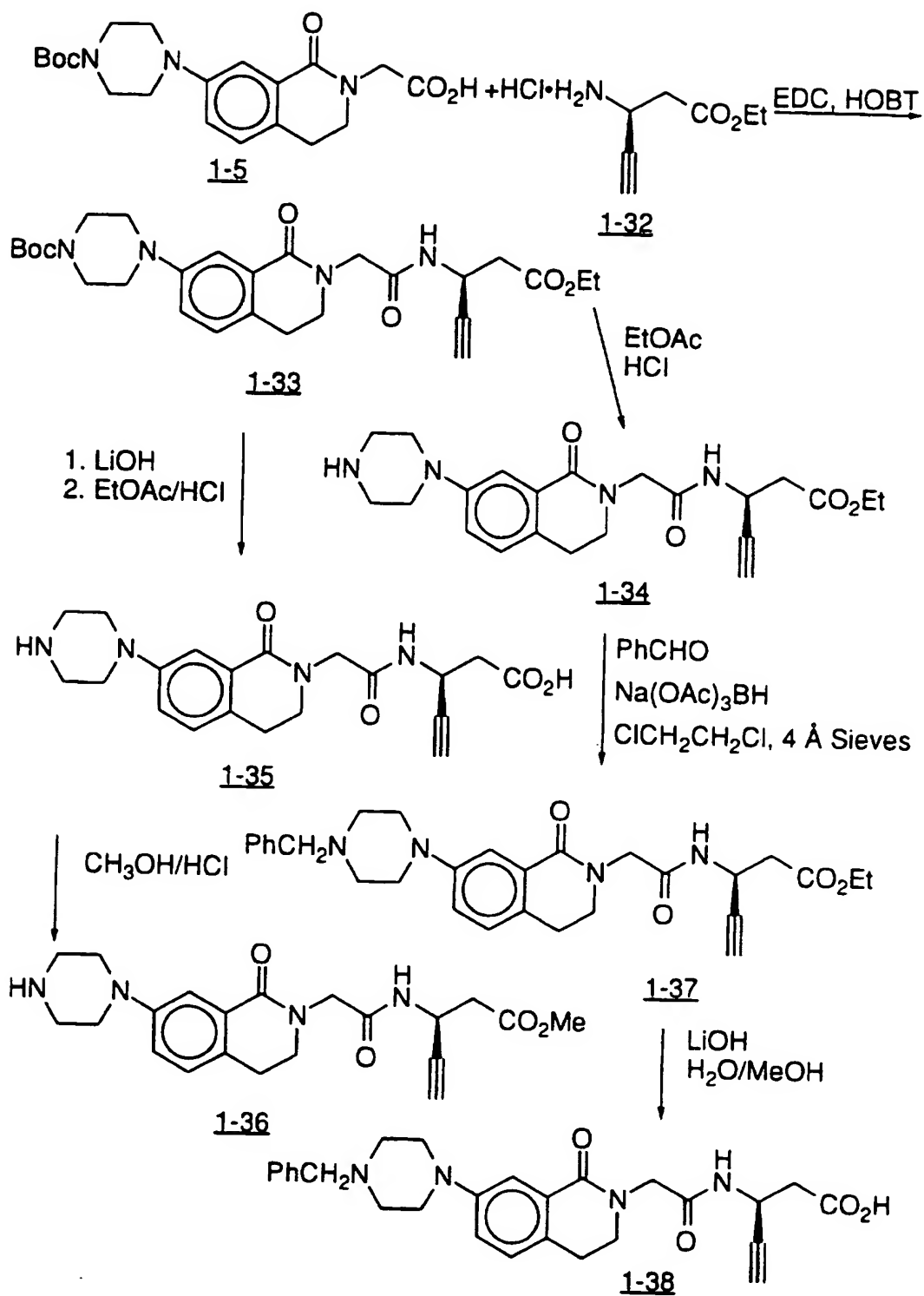
Anal. Calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_4\text{O}_4\text{F} \cdot 1.6 \text{ TFA}$

C, 51.29; H, 4.53; N, 8.80

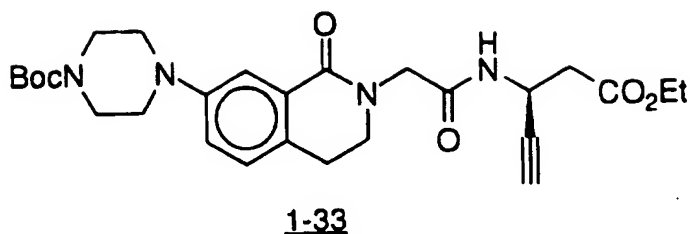
found C, 51.34; H, 4.48; N, 8.80

25

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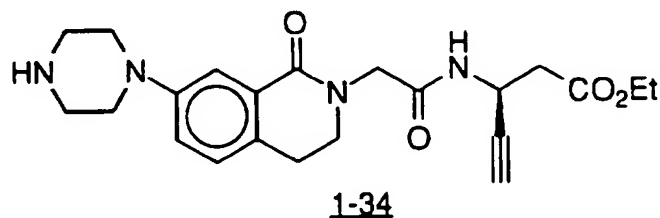


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N-([7-(4-N-Boc-Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(S)-(ethynyl)-β-alanine ethyl ester (1-33)

- 5 To a solution of 1-5 (150 mg, 0.39 mmol), HOBt (63 mg, 0.46 mmol) and EDC (111 mg, 0.58 mmol) was added 3(S)-(ethynyl)-β-alanine ethyl ester hydrochloride (1-32) (U.S. Patent 5,272,162; 82 mg, 0.46 mmol) and Et₃N (80.7 μl, 0.58 mmol). The mixture was stirred at room temperature under argon for 16 hours and then partitioned between
- 10 EtOAc and 10% citric acid. The aqueous phase was extracted with EtOAc (x3) and the combined organic layers then washed with saturated aqueous NaHCO₃ followed by brine. Removal of the dried (MgSO₄) solvent afforded a yellow oil which was purified by column chromatography (silica gel; hexane/EtOAc 1:1) to give 1-33 as an oil.
- 15 R_f (silica; EtOAc/hexane 2:1) 0.57



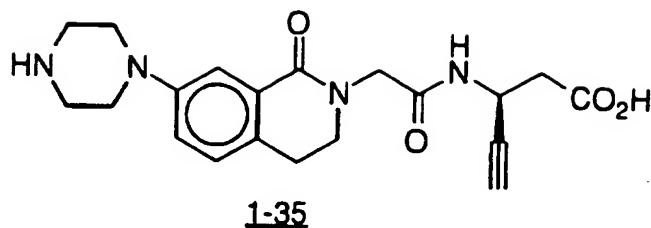
- 20 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(S)-(ethynyl)-β-alanine ethyl ester (1-34)

HCl (g) was bubbled through a solution of 1-33 (176 mg, 0.37 mmol) in 50 ml of EtOAc for 5 minutes. The solvent was removed *in vacuo* to leave 1-34 as the HCl salt.

FAB mass spectrum m/z = 413 (m+1).

- 25 Anal. calcd. for C₂₂ H₂₈ N₄ O₄ 2.65 HCl
 C, 51.89; H, 6.07; N, 11.00
 found C, 51.93; H, 6.04; N, 10.70

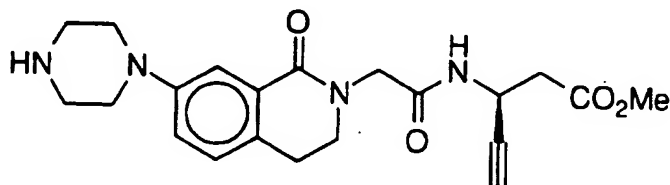
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N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(S)-(ethynyl)-β-alanine (1-35)

- 5 The ester 1-33 (70 mg, 0.16 mmol) was stirred in 10 ml MeOH and 0.65 ml 1N LiOH for 16 hours and then 1N HCl was added to give pH = 4. After removal of the solvent the residue was purified by reverse phase HPLC (C18 column, H₂O/CH₃CN with 0.1% TFA, gradient) to give 1-35 as the TFA salt.

- 10 FAB mass spectrum m/z = 385 (m+1)
Anal. calcd. for C₂₀H₂₄N₄O₄ 1.6 • TFA
C, 49.16; H, 4.55; N, 9.88
found C, 49.06; H, 4.59; N, 10.07

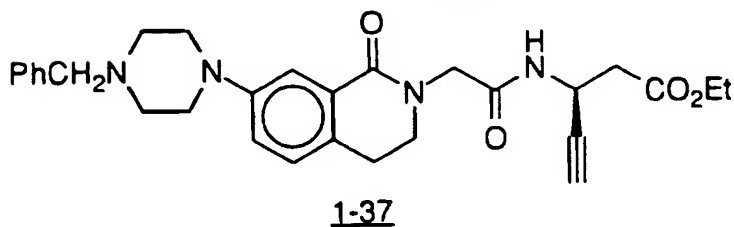
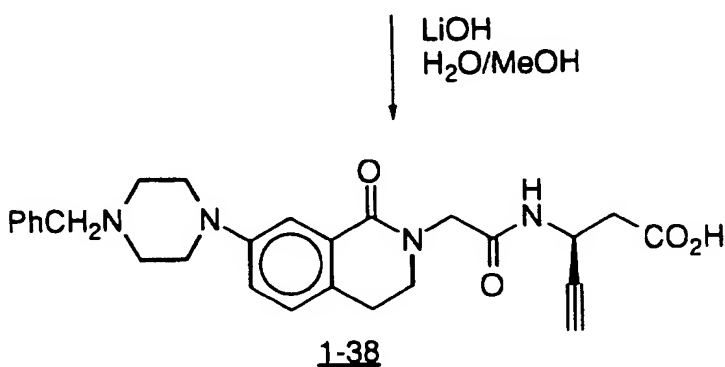
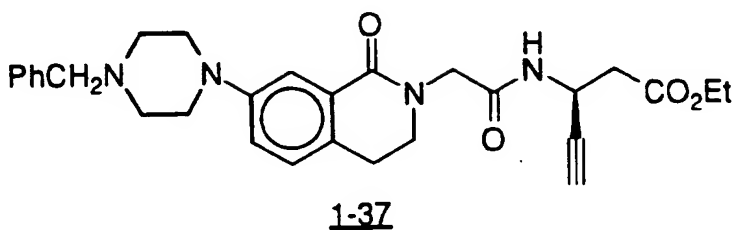
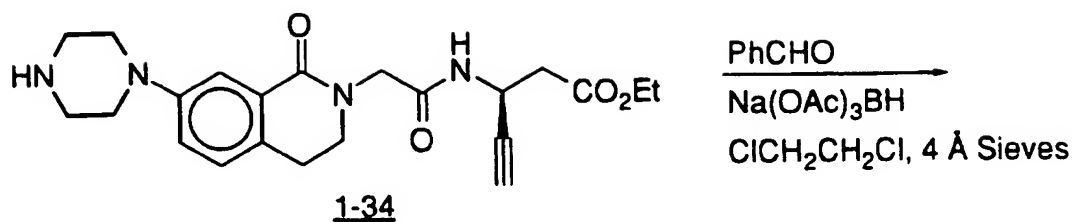


- 15 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(S)-(alkynyl)-β-alanine methyl ester (1-36)

- A solution of 1-35 in methanol was treated with HCl gas. After 1 hour, the solvent was removed and the residue was purified by reverse phase HPLC (C18 column, H₂O/CH₃CN with 0.1% TFA, gradient) to give 1-36 as the TFA salt.

- 20 FAB mass spectrum m/z = 399 (m+1)
Anal. calcd. for C₂₁H₂₆N₄O₄ • 1.80 TFA
C, 48.94; H, 4.64; N, 9.28
25 found C, 48.94; H, 4.72; N, 9.31

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5 N-([7-(4-Benzylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(S)-(alkynyl)-β-alanine ethyl ester (1-37)

A solution of 1-34 (213 mg, 0.48 mmol), benzaldehyde (58 μL , 0.57 mmol), $\text{NaBH}(\text{OAc})_3$ (303 mg, 1.43 mmol) and Et_3N (66.5 μL , 0.48 mmol) in 1,2-dichloroethane (4 ml) with 4 Å molecular sieves was stirred for 3 days. The mixture was filtered through celite, poured into NaHCO_3 (saturated solution) and extracted with EtOAc (x2). After
 10 washing the organic layers with brine, drying (MgSO_4) and filtration the solvent was removed to give an oil. Purification by silica gel

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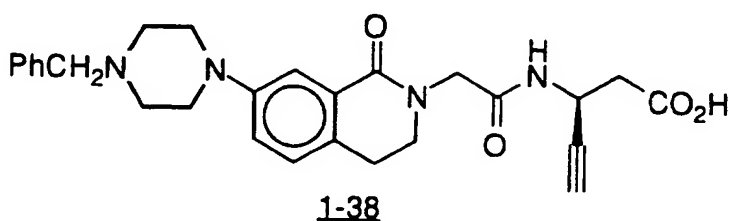
chromatography (EtOAc) afforded 1-37 which was converted to the HCl salt by treatment with 0.1% HCl solution and then lyophilization.

FAB mass spectrum $m/z = 503 (m+1)$

Anal. calcd. for $C_{29}H_{34}N_4O_4 \cdot 1.6 HCl$

5 C, 62.09; H, 6.40; N, 9.99

found C, 62.15; H, 6.35; N, 9.77.



10 N-{[7-(4-Benzylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl}-3(S)-(alkynyl)-β-alanine (1-38)

1-37 was hydrolysed in aqueous LiOH/NaOH according to the procedure described for 1-5. Purification by reverse phase HPLC (C18 column; H₂O/CH₃CN with 0.1% TFA, gradient) to give 1-38 as the

15 TFA salt.

FAB mass spectrum $m/z = 475 (m+1)$

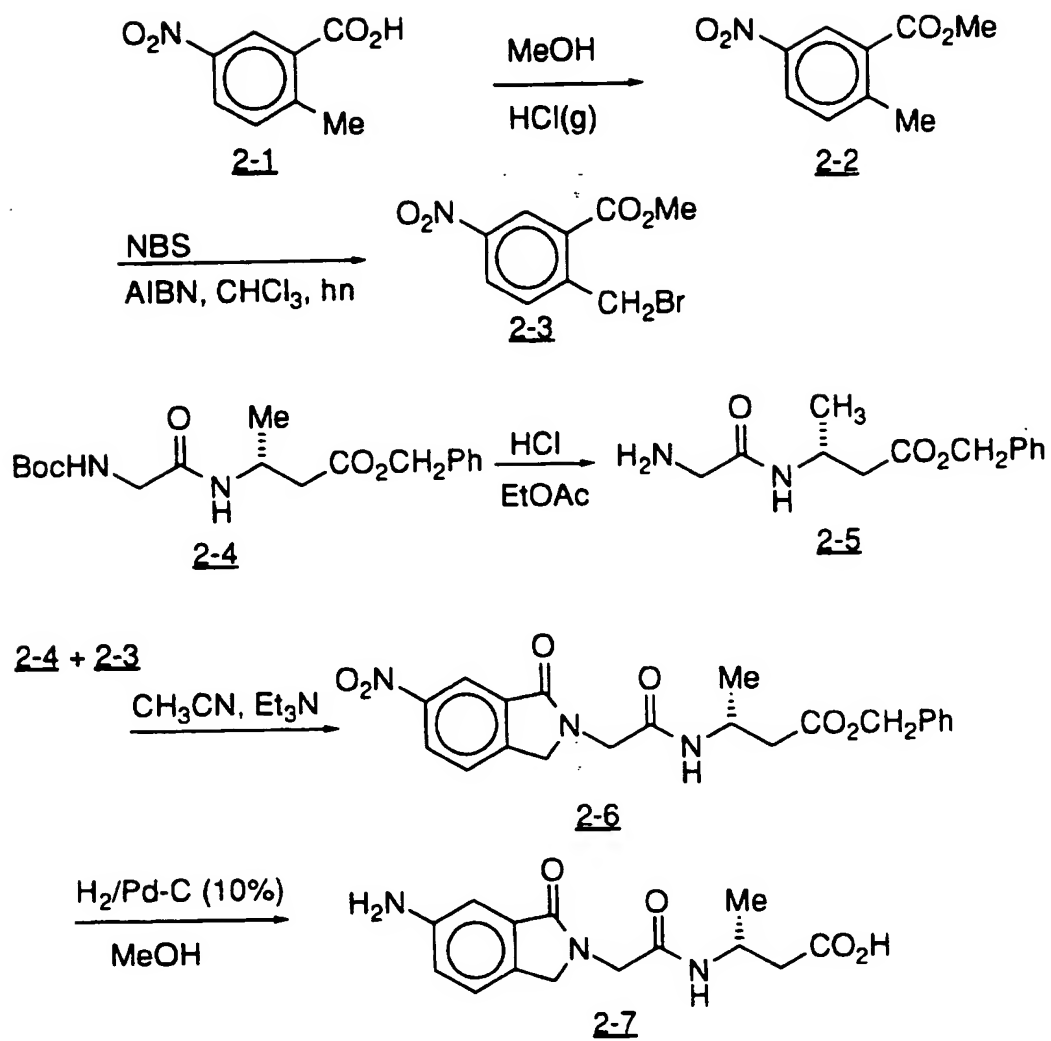
Anal. calcd. for $C_{27}H_{30}N_4O_4 \cdot 1.4 TFA$

C, 56.44; H, 4.99; N, 8.83

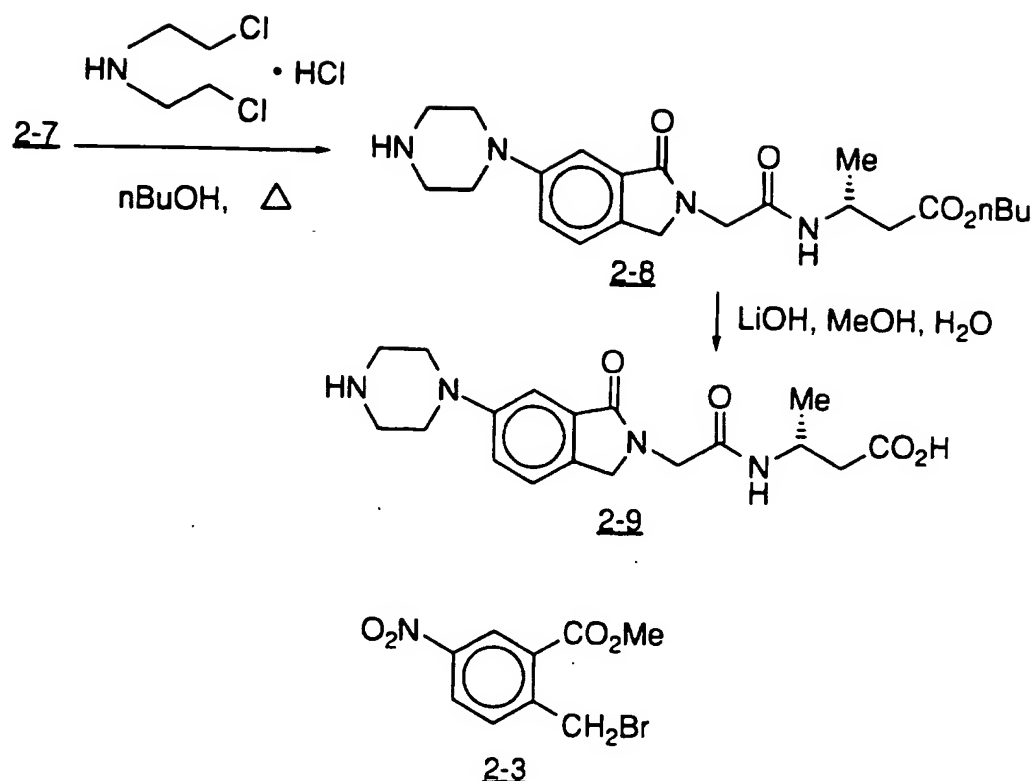
found C, 56.49; H, 5.01; N, 8.86.

20

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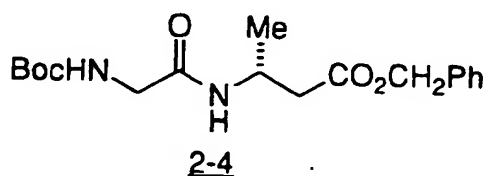
SCHEME 2

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5 Methyl 6-Bromomethyl-3-nitrobenzoate (2-3)

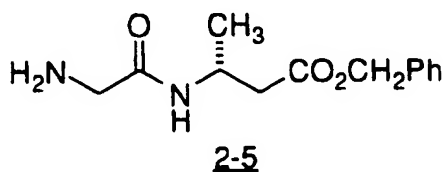
3-Nitro-6-methylbenzoic acid (2-1) (Aldrich) was converted into methyl 3-nitro-6-methylbenzoate (2-2) using the standard procedure of MeOH and HCl gas. To a mixture of methyl 3-nitro-6-methylbenzoate (2-2) (2.0 g, 10.3 mmol) and N-bromosuccinimide (1.64 g, 9.23 mmol) in CHCl₃ was added AIBN (20 mg) and this was then photolysed at reflux for 4 hours. The reaction was cooled, filtered and the filtrate evaporated to dryness. Chromatography of the residue (silica, hexane/EtOAc 92:8) afforded 2-3 as a solid (1.56 g). *R*_f (silica; hexane/EtOAc 10:1) = 0.25.



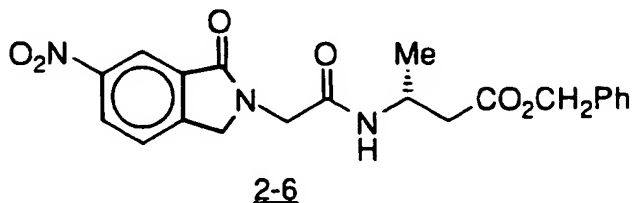
- 54 -

N-t-Butoxycarbonylglycyl-3(R)-methyl-β-alanine benzyl ester (2-4)

N-t-Butoxycarbonylglycine was coupled with 3(R)-methyl-β-alanine benzyl ester • 0.5 H₂SO₄ (1-10) (Celgene) using the conditions described for 1-7, to give 2-4 after chromatography (silica; hexane/EtOAc 2:3). R_f (silica; hexane/EtOAc 1:1) = 0.3.

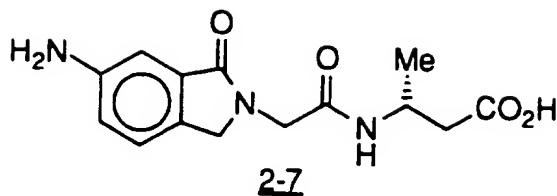
N-Glycyl-3(R)-methyl-β-alanine benzyl ester hydrochloride (2-5)

N-t-Butoxycarbonylglycyl-3(R)-methyl-β-alanine benzyl ester 2-4 (3.32 g) in EtOAc (100 mL) cooled to -60°C was treated with HCl gas until saturated. The mixture was stirred for 30 minutes then the solvent was removed and the residue triturated with ether to give 2-5 as a solid.

N-[[6-Nitro-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl]-3(R)-methyl-β-alanine benzyl ester (2-6)

Methyl 6-bromomethyl-3-nitrobenzoate (430 mg, 1.64 mmol), N-glycyl-3(R)-methyl-β-alanine benzyl ester hydrochloride 2-4 (611 mg, 2.13 mmol) and triethylamine (0.68 mL, 4.92 mmol) were stirred in acetonitrile (10 mL) for 16 hours. The solution was poured into 1N HCl and extracted with EtOAc (3x), washed with brine, dried (MgSO₄) and evaporated. Purification by column chromatography eluting with EtOAc afforded 2-6 as a solid. R_f (silica; EtOAc) = 0.45.

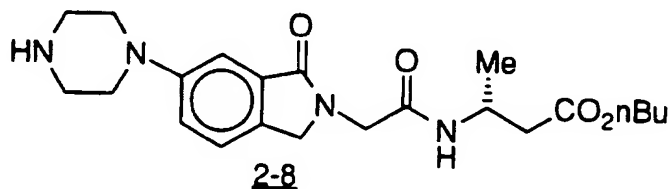
- 55 -



N-([6-Amino-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl)-3(R)-methyl- β -alanine (2-7)

5 A solution of N-([6-nitro-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl)-3(R)-methyl- β -alanine benzyl ester (2-6) (374 mg) in MeOH (35 mL) was purged with argon and then 10% Pd on carbon was added. The mixture was placed under an atmosphere of H₂ (balloon) and stirred for 16 hours. After filtration through celite, the solvent was removed to give 2-7 as a solid. FAB mass spectrum m/z = 292 (M+1).

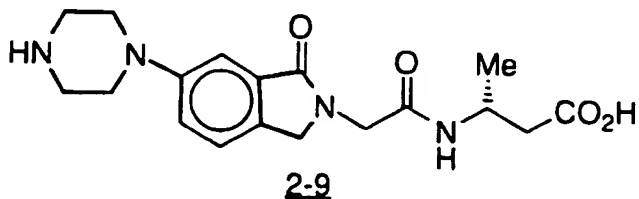
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N-([6-(Piperazin-1-yl)-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl)-3(R)-methyl- β -alanine n-butyl ester (2-8)

15 N-([6-Amino-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl)-3(R)-methyl- β -alanine (2-7) (203 mg, 0.7 mmol) and bis(2-chloroethyl)amine hydrochloride (137 mg, 0.77 mmol) in n-butanol (10 mL) were heated at 110°C for 3 days. The solvent was removed and the residue chromatographed (EtOH/H₂O/NH₄OH 10:0.5:0.5) to give 2-8. R_f (silica; EtOH/H₂O/NH₄OH 10:0.5:0.5) = 0.61.

20



25 N-([6-(Piperazin-1-yl)-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl)-3(R)-methyl- β -alanine (2-9)

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The ester 2-8 (150 mg, 0.36 mmol), 1N LiOH (1.08 mL, 1.08 mmol) and MeOH (5 mL) were stirred for 16 hours. The pH was adjusted to ~pH 5 and the MeOH was removed in vacuo to give an aqueous solution which was purified by reverse phase HPLC (C18 column, H₂O/CH₃CN with 0.1% TFA, gradient) to give 2-9 as the TFA salt.

FAB mass spectrum $m/z = 361$ (M+1)

Anal. Calcd for C₁₈H₂₄N₄O₄ • 2.0 TFA • 1.6 H₂O • 0.3 CH₃CN

C, 43.11; H, 4.82; N, 9.57

10 found C, 43.10; H, 4.76; N, 9.71

Therapeutic Treatment

Compounds of the invention may be administered to patients where inhibition of human or mammalian platelet aggregation or adhesion is desired.

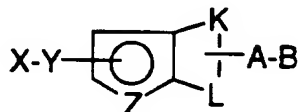
15 Compounds of the invention are useful in inhibiting platelet aggregation and thus, they may find utility in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of the invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

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WHAT IS CLAIMED IS:

1. A fibrinogen receptor antagonist of the following formula

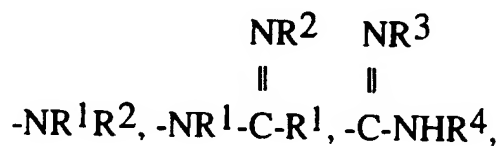
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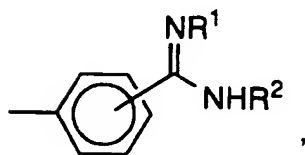
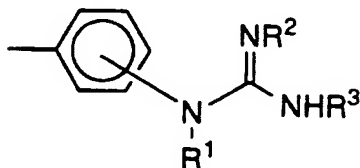
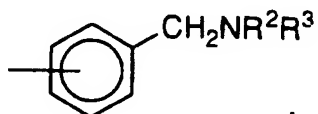
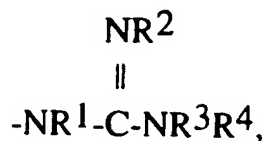
and pharmaceutically acceptable salts thereof, where

X is chosen from the group consisting of:

10



15



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and a 5- to 6-membered mono- or bicyclic aromatic or nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O and S and either unsubstituted or substituted with R¹, R², R³ or R⁴,

5 wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen,

C₁-10 alkyl,

aryl C₀-8 alkyl,

oxo,

10 thio,

amino C₀-8 alkyl, C₁-3 acylamino C₀-8 alkyl,

C₁-6 alkylamino C₀-8 alkyl,

C₁-6 dialkylamino C₀-8 alkyl,

C₁-4 alkoxy C₀-6 alkyl,

15 carboxy C₀-6 alkyl,

C₁-3 alkoxycarbonyl C₀-6 alkyl,

C₁-4 alkylthio C₀-6 alkyl,

aryl C₀-4 thio C₀-6 alkyl,

carboxy C₀-6 alkyloxy, and

20 hydroxy C₀-6 alkyl;

Z is chosen from the group consisting of:

-CR¹=CR²-,

-CR¹=N-,

25 -N=CR¹-, and

S, O, and NR¹;

Y and A are independently chosen from the group consisting of

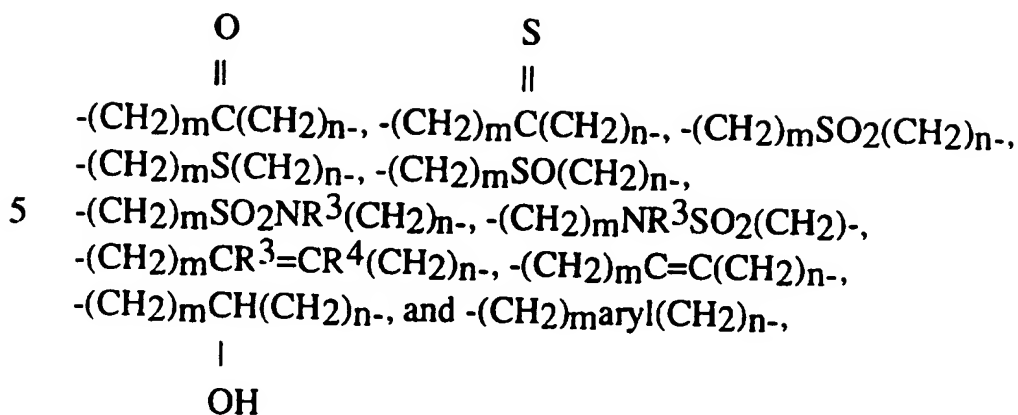
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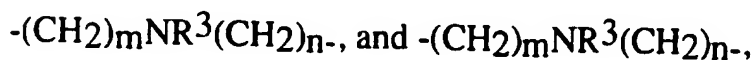
-(CH₂)_m-, -(CH₂)_mCNR³(CH₂)_n-, -(CH₂)_mNR³C(CH₂)_n-,

-(CH₂)_mO(CH₂)_n-,

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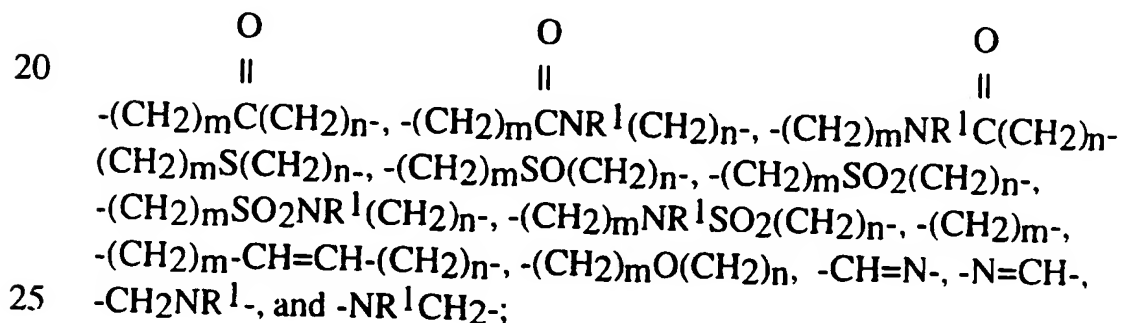
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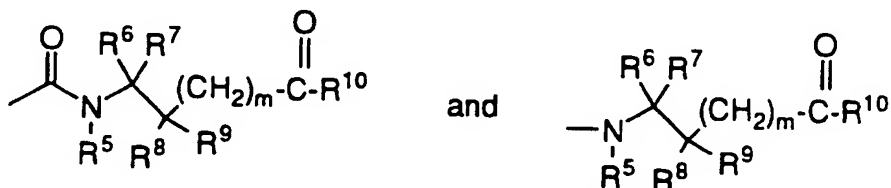
where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising K and L, and Y is attached to a ring atom of the ring comprising Z;

15

K and L are independently chosen from the group consisting of:



B is chosen from the group consisting of:



where m = 0-2, and

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where R5, R6, R7, R8 and R9 are independently chosen from the group consisting of:

- hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl,
- C₀₋₆ alkyl-CH = CH-C₀₋₆ alkyl,
- 5 -C₀₋₆ alkyl-CH = CH-C₀₋₆ alkylaryl,
- C₀₋₆ alkyl-C \equiv C-C₀₋₆ alkyl,
- C₀₋₆ alkyl-C \equiv C-C₀₋₆ alkylaryl,
- hydroxy C₁₋₆ alkyl, carboxy C₀₋₆ alkyl,
- C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl, aryl C₁₋₆ alkyloxy,
- 10 aryl C₀₋₆ alkyl, C₁₋₆ alkylcarbonyloxy,
- C₀₋₆ alkylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylamino C₀₋₆ alkyl,
- C₀₋₆ dialkylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonyloxy,
- 15 C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
- C₁₋₆ alkylaminocarbonyloxy,
- aryl C₀₋₆ alkylaminocarbonyloxy,
- aryl C₀₋₈ alkylsulfonylamino C₀₋₆ alkyl,
- C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
- 20 aryl C₀₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
- C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- 25 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
- aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
- C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
- 30 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
- C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylthiocarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminocarbonyl C₀₋₆ alkyl, and
- aryl C₀₋₈ alkylaminocarbonyl C₀₋₆ alkyl,

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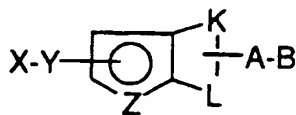
unsubstituted or substituted with one or more substituents selected from R¹ and R², and

5 $\begin{array}{c} \text{O} \\ \parallel \\ \text{C-AA} \end{array}$, where AA is an L- or D-amino acid, or its corresponding ester, connected through an amide linkage;

R¹⁰ is chosen from the group consisting of:
 10 hydroxy,
 C₁-8 alkyloxy,
 aryl C₀-6 alkyloxy,
 C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 aryl C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 15 C₁-8 alkylaminocarbonyl C₁-4 alkyloxy,
 C₁-8 dialkylaminocarbonyl C₁-4 alkyloxy, and
 an L- or D- amino acid joined by an amide linkage, wherein the carboxylic acid moiety of said amino acid is as the free acid or is esterified by C₁-6 alkyl.

20

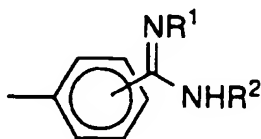
2. A compound of Claim 1 having the formula



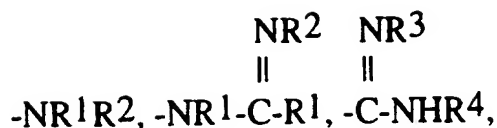
and pharmaceutically acceptable salts thereof, where

25

X is chosen from the group consisting of:



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- 5 $\begin{array}{c} \text{NR}^2 \\ \parallel \\ -\text{NR}^1-\text{C}-\text{NR}^3\text{R}^4, \end{array}$ and a 5- to 6- membered mono- or bicyclic nonaromatic ring system containing 0, 1, or 2 heteroatoms selected from N, O, and S and either unsubstituted or substituted with R¹, R², R³
- 10 and R⁴, wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen,
- C₁₋₁₀ alkyl,
- C₁₋₄ alkoxy C₀₋₆ alkyl,
- carboxy C₀₋₆ alkyl, C₁₋₃ alkoxycarbonyl C₀₋₆ alkyl,
- 15 carboxy C₀₋₆ alkyloxy,
- hydroxy C₀₋₆ alkyl,
- C₁₋₄ alkythio C₀₋₆ alkyl,
- aryl C₀₋₄ thio C₀₋₆ alkyl,
- amino C₀₋₃ alkyl,
- 20 C₁₋₆ alkylamino C₀₋₃ alkyl, and
- C₁₋₆ acylamino C₀₋₃ alkyl;

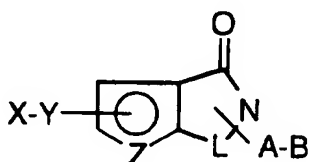
Y and A are independently chosen from the group consisting of:

- 25 $\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ -(\text{CH}_2)_m-, -(\text{CH}_2)_m\text{CNR}^3(\text{CH}_2)_n-, -(\text{CH}_2)_m\text{NR}^3\text{C}(\text{CH}_2)_n-, \\ -(\text{CH}_2)_m\text{O}(\text{CH}_2)_n-, -(\text{CH}_2)_m\text{S}(\text{CH}_2)_n-, -(\text{CH}_2)_m\text{SO}_2\text{NR}^3(\text{CH}_2)_n-, \\ -(\text{CH}_2)_m\text{CR}^3=\text{CR}^4(\text{CH}_2)_n-, \text{ and} \end{array}$
- 30 $\begin{array}{c} \text{O} \\ \parallel \\ -(\text{CH}_2)_m\text{C}(\text{CH}_2)_n-, \end{array}$

- 63 -

where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising K and L, and Y is attached to a ring atom of the ring comprising Z.

- 5 3. A compound of Claim 2 having the formula



and pharmaceutically acceptable salts thereof, where

Z is chosen from the group consisting of:

10

-CR¹=CR²-, -C=NR¹-, -N=CR¹-, and S

Y and A are independently chosen from the group consisting of:

15

$$\begin{array}{ccc} \text{O} & & \text{O} \\ \parallel & & \parallel \end{array}$$

-(CH₂)_m-, -(CH₂)_mCNR³(CH₂)_n-, -(CH₂)_mNR³C(CH₂)_n-,

20

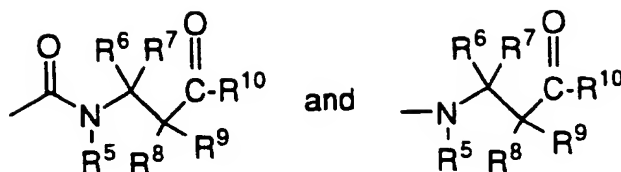
$$\begin{array}{c} \text{O} \\ \parallel \end{array}$$

-(CH₂)_mO(CH₂)_n-, -(CH₂)_mC(CH₂)_n-, -(CH₂)_mSO₂(CH₂)_n-, and
 -(CH₂)_mSO₂NR³(CH₂)_n-,

25 where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising L, and Y is attached to a ring atom of the ring comprising Z;

B is chosen from the group consisting of:

- 64 -



where R₅, R₆, R₇, R₈ and R₉ are independently chosen from:

- hydrogen, fluorine, C₁-8 alkyl, hydroxyl,
- 5 hydroxy C₁-6 alkyl,
- C₀-6 alkyl -CH = CH-C₀-6 alkyl,
- C₀-6 alkyl -CH = CH-C₀-6 alkylaryl,
- C₀-6 alkyl -C ≡ C-C₀-6 alkyl,
- C₀-6 alkyl -C ≡ C-C₀-6 alkylaryl,
- 10 carboxy C₀-6 alkyl, C₁-6 alkyloxy, C₃-8 cycloalkyl,
- aryl C₀-6 alkyl,
- C₁-6 alkylcarbonyloxy, C₀-6 alkylamino C₀-6 alkyl,
- aryl C₀-6 alkylcarbonyloxy,
- C₀-6 dialkylamino C₀-6 alkyl,
- 15 C₁-6 alkylaminocarbonyloxy,
- aryl C₁-6 alkylaminocarbonyloxy,
- C₁-8 alkylsulfonylamino C₀-6 alkyl,
- aryl C₀-6 alkylsulfonylamino C₀-6 alkyl,
- C₁-8 alkyloxycarbonylamino C₀-8 alkyl,
- 20 C₁-8 alkylcarbonylamino C₀-6 alkyl,
- aryl C₀-6 alkylcarbonylamino C₀-6 alkyl,
- C₀-8 alkylaminocarbonylamino C₀-6 alkyl,
- aryl C₀-8 alkylaminocarbonylamino C₀-6 alkyl,
- C₀-8 alkylaminosulfonylamino C₀-6 alkyl,
- 25 aryl C₀-8 alkylaminosulfonylamino C₀-6 alkyl,
- C₁-6 alkylsulfonyl C₀-6 alkyl,
- aryl C₀-6 alkylsulfonyl C₀-6 alkyl,
- C₁-6 alkylcarbonyl C₀-6 alkyl,
- aryl C₀-6 alkylcarbonyl C₀-6 alkyl,
- 30 C₁-6 alkylthiocarbonylamino C₀-6 alkyl; and

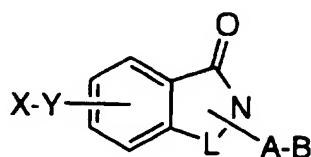
- 65 -

R¹⁰ is chosen from the group consisting of:

hydroxy,
C₁₋₈ alkyloxy, and
aryl C₀₋₆ alkyloxy.

5

4. A compound of Claim 3 having the formula



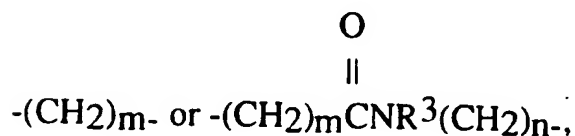
and pharmaceutically acceptable salts thereof, where

10 L is chosen from the group consisting of:

-CH₂- or -(CH₂)₂-;

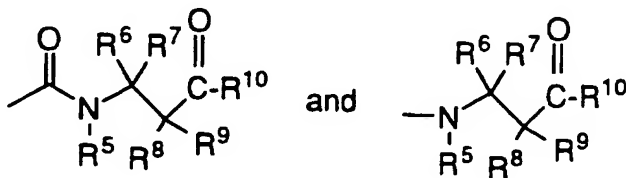
Y and A are independently chosen from the group consisting of:

15



20 where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising L;

B is chosen from the group consisting of:



25

where R⁵, R⁶, R⁷, R⁸ and R⁹ are independently chosen from:
hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl,

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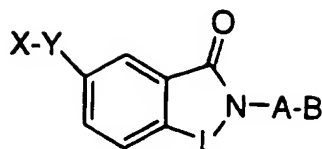
- hydroxy C₁₋₆ alkyl,
 -C₀₋₆ alkyl -CH = CH-C₀₋₆ alkyl,
 -C₀₋₆ alkyl -CH = CH-C₀₋₆ alkylaryl,
 -C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkyl,
 5 -C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkylaryl,
 carboxy C₀₋₆ alkyl, C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl,
 aryl C₀₋₆ alkyl,
 C₁₋₆ alkylcarbonyloxy, C₀₋₆ alkylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonyloxy,
 10 C₀₋₆ dialkylamino C₀₋₆ alkyl,
 C₁₋₆ alkylaminocarbonyloxy,
 aryl C₁₋₆ alkylaminocarbonyloxy,
 C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
 15 C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
 C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
 C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 20 C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
 aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
 C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
 25 aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
 C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl; and

R¹⁰ is chosen from the group consisting of:

- hydroxy,
 30 C₁₋₈ alkyloxy, and
 aryl C₀₋₆ alkyloxy.

5. A compound of Claim 4 having the formula

- 67 -



and pharmaceutically acceptable salts thereof, where

5 X is a 6-membered monocyclic nonaromatic ring containing 0, 1 or 2 N heteroatoms either unsubstituted or substituted with R^1 , R^2 , R^3 or R^4 , wherein R^1 , R^2 , R^3 and R^4 are independently selected from the group consisting of hydrogen,

10 C₁-10 alkyl,
C₁-4 alkoxy C₀-6 alkyl,
carboxy C₀-6 alkyl, C₁-3 alkoxycarbonyl C₀-6 alkyl,
carboxy C₀-6 alkyloxy,
hydroxy C₀-6 alkyl,
C₁-4 alkythio C₀-6 alkyl,
15 aryl C₀-4 thio C₀-6 alkyl,
amino C₀-3 alkyl,
C₁-6 alkylamino C₀-3 alkyl, and
C₁-6 acylamino C₀-3 alkyl;

20 L is chosen from the group consisting of:

-CH₂- or -(CH₂)₂;

Y and A are independently chosen from the group consisting of:

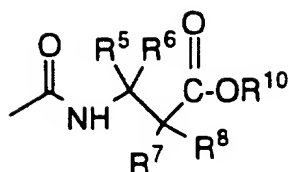
25

O
||
-(CH₂)_m- or -(CH₂)_mCN R^3 (CH₂)_n-,

30 where m and n are integers independently chosen from 0-6, wherein A is attached to a ring atom of the ring comprising L;

B is chosen from the group consisting of:

- 68 -



- where R⁵, R⁶, R⁷, R⁸ and R⁹ are independently chosen from:
- hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl,
 - 5 hydroxy C₁₋₆ alkyl,
 - C₀₋₆ alkyl -CH = CH-C₀₋₆ alkyl,
 - C₀₋₆ alkyl -CH = CH-C₀₋₆ alkylaryl,
 - C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkyl,
 - C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkylaryl,
 - 10 carboxy C₀₋₆ alkyl, C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl,
 - aryl C₀₋₆ alkyl,
 - C₁₋₆ alkylcarbonyloxy, C₀₋₆ alkylamino C₀₋₆ alkyl,
 - aryl C₀₋₆ alkylcarbonyloxy,
 - C₀₋₆ dialkylamino C₀₋₆ alkyl,
 - 15 C₁₋₆ alkylaminocarbonyloxy,
 - aryl C₁₋₆ alkylaminocarbonyloxy,
 - C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
 - aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
 - C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
 - 20 C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
 - aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
 - C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 - aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
 - C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 - 25 aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
 - C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,
 - aryl C₀₋₆ alkylsulfonyl C₀₋₆ alkyl,
 - C₁₋₆ alkylcarbonyl C₀₋₆ alkyl,
 - aryl C₀₋₆ alkylcarbonyl C₀₋₆ alkyl,
 - 30 C₁₋₆ alkylthiocarbonylamino C₀₋₆ alkyl; and

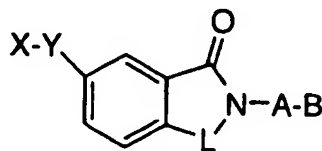
- 69 -

R¹¹ is chosen from the group consisting of:

hydroxy,
C₁₋₈ alkyloxy, and
aryl C₀₋₆ alkyloxy.

5

6. A compound of Claim 5 having the formula



and pharmaceutically acceptable salts thereof, where

10 X is a 6-membered monocyclic nonaromatic ring containing 0, 1 or 2 N heteroatoms either unsubstituted or substituted with R¹, R², R³ or R⁴, wherein R¹, R², R³ and R⁴ are independently selected from the group consisting of hydrogen,

15 C₁₋₁₀ alkyl,
C₁₋₄ alkoxy C₀₋₆ alkyl,
carboxy C₀₋₆ alkyl, C₁₋₃ alkoxy carbonyl C₀₋₆ alkyl,
carboxy C₀₋₆ alkyloxy,
hydroxy C₀₋₆ alkyl,
20 C₁₋₄ alkythio C₀₋₆ alkyl,
aryl C₀₋₄ thio C₀₋₆ alkyl,
amino C₀₋₃ alkyl,
C₁₋₆ alkylamino C₀₋₃ alkyl, and
C₁₋₆ acylamino C₀₋₃ alkyl;

25 L is chosen from the group consisting of:

-CH₂- or -(CH₂)₂-;

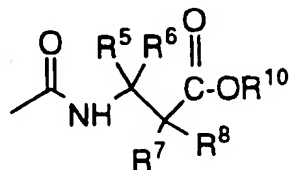
30 Y and A are independently chosen from the group consisting of:

-(CH₂)_m-,

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where m is an integer independently chosen from 0 and 1, wherein A is attached to a ring atom of the ring comprising L;

B is chosen from the group consisting of:



5

where R⁵, R⁶, R⁷, R⁸ and R⁹ are independently chosen from:

- hydrogen, fluorine, C₁₋₈ alkyl, hydroxyl,
- hydroxy C₁₋₆ alkyl,
- C₀₋₆ alkyl -CH = CH-C₀₋₆ alkyl,
- C₀₋₆ alkyl -CH = CH-C₀₋₆ alkylaryl,
- C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkyl,
- C₀₋₆ alkyl -C ≡ C-C₀₋₆ alkylaryl,
- carboxy C₀₋₆ alkyl, C₁₋₆ alkyloxy, C₃₋₈ cycloalkyl,
- aryl C₀₋₆ alkyl,
- C₁₋₆ alkylcarbonyloxy, C₀₋₆ alkylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonyloxy,
- C₀₋₆ dialkylamino C₀₋₆ alkyl,
- C₁₋₆ alkylaminocarbonyloxy,
- aryl C₁₋₆ alkylaminocarbonyloxy,
- C₁₋₈ alkylsulfonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylsulfonylamino C₀₋₆ alkyl,
- C₁₋₈ alkyloxycarbonylamino C₀₋₈ alkyl,
- C₁₋₈ alkylcarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₆ alkylcarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminocarbonylamino C₀₋₆ alkyl,
- C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- aryl C₀₋₈ alkylaminosulfonylamino C₀₋₆ alkyl,
- C₁₋₆ alkylsulfonyl C₀₋₆ alkyl,

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aryl C0-6 alkylsulfonyl C0-6 alkyl,
C1-6 alkylcarbonyl C0-6 alkyl,
aryl C0-6 alkylcarbonyl C0-6 alkyl,
C1-6 alkylthiocarbonylamino C0-6 alkyl; and

5

R¹⁰ is chosen from the group consisting of:

hydroxy,
C1-8 alkyloxy, and
aryl C0-6 alkyloxy.

10

7. A compound of Claim 1 selected from the group consisting of:

15 N-[[7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl]-
3(S)-(3-pyridyl)- β -alanine,

N-[[7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl]-
3(S)-(3-pyridyl)- β -alanine ethyl ester,

20 N-[[7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl]-
3(R)-methyl- β -alanine,

N-[[7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl]-
 β -alanine.

25

N-[[7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl]-
3(R)-(2-phenethyl)- β -alanine,

30 N-[[7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl]-
2(S)-(phenylsulfonylamino)- β -alanine,

8. A compound of Claim 1 selected from the group consisting of:

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- N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(S)-(3-pyridyl)- β -alanine,
- 5 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(S)-(3-pyridyl)- β -alanine ethyl ester,
- N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(R)-methyl- β -alanine,
- 10 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
 β -alanine,
- N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(R)-(2-phenethyl)- β -alanine,
- 15 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
2(S)-(phenylsulfonylamino)- β -alanine,
- N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
20 2(R)-(phenylsulfonylamino)- β -alanine,
- N-([6-(Piperazin-1-yl)-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl)-3(R)-
methyl- β -alanine n-butyl ester,
- 25 N-([6-(Piperazin-1-yl)-2,3-dihydro-1(1H)-isoindolone-2-yl]acetyl)-3(R)-
methyl- β -alanine.
- N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(R)-methyl- β -alanine ethyl ester,
- 30 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-
3(R)-(2-chlorobenzyl)- β -alanine,

- 73 -

N-([7-(4-Benzylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(R)-2(2-chlorobenzyl)- β -alanine ethyl ester,

5 N-([7-(4-Benzylpiperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(R)-(2-chlorobenzyl)- β -alanine,

N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3-(3-fluorophenyl)- β -alanine,

10 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(R)-(ethynyl)- β -alanine ethyl ester, and

15 N-([7-(Piperazin-1-yl)-3,4-dihydro-1(1H)-isoquinolinone-2-yl]acetyl)-3(R)-(ethynyl)- β -alanine.

9. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

20 10. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 9.

25 11. A composition for inhibiting the aggregation of blood platelets in a mammal, comprising a compound of Claim 1 in combination with two or more agents selected from a thrombolytic agent, an anticoagulant agent, and an antiplatelet agent and a pharmaceutically acceptable carrier.

30 12. A method for inhibiting the aggregation of blood platelets in a mammal, comprising administering to mammal the composition of Claim 11.

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13. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

5 14. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 13.

10 15. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 3 and a pharmaceutically acceptable carrier.

15 16. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 15.

20 17. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 4 and a pharmaceutically acceptable carrier.

18. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 17.

25 19. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 5 and a pharmaceutically acceptable carrier.

30 20. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 19.

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21. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 6 and a pharmaceutically acceptable carrier.
- 5 22. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 21.
- 10 23. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising a compound of Claim 7 and a pharmaceutically acceptable carrier.
- 15 24. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a composition of Claim 23.
- 20 25. The use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/02093

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NoneElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A 94/14776 (SMITHKLINE BEECHAM CORPORATION) 07 July 1994, see entire document, especially pages 3-4, 26.	1-2, 7-14
Y	US, A, 5,334,596 (HARTMAN ET AL,) 02 August 1994, see entire document, especially columns 3-4.	1-25

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

07 MAY 1996

Date of mailing of the international search report

14 JUN 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

ANTHONY BOTTINO

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/02093

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: - -

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-25

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/02093

A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C07D 209/02, 209/36, 209/42, 209/12, 209/18, 209/04, 209/48, 217/22, 217/18, 217/00, 215/16, 215/38, 215/12, 487/00, 225/02; A61K 31/55, 31/47, 31/405, 31/40

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

514/221, 307, 310, 313, 415, 416; 540/463, 523; 546/141, 143, 146, 149, 151, 153, 159, 156, 174; 548/483, 484, 492, 494, 495, 503, 509, 510, 514

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/221, 307, 310, 313, 415, 416; 540/463, 523; 546/141, 143, 146, 149, 151, 153, 159, 156, 174; 548/483, 484, 492, 494, 495, 503, 509, 510, 514

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

Since this is an international application, the unity of invention standard of PCT Rule 13 and 37 CFR 1.475 was applied in this case.

- I. Claims 1-25 wherein Z in the bicyclic compound is CR1=CR2 completing a 6-membered carbocycle.
- II. Claims 1-3, 9-15, 24 wherein Z in the bicyclic compound is CR1=N- or -N=CR1 completing a 6-membered heterocycle.
- III. Claims 1-3, 9-15, 24 wherein Z in the bicyclic compound is S completing a 5-membered heterocycle.
- IV. Claims 1-2, 9-15, 24 wherein Z in the bicyclic compound is O completing a 5-membered heterocycle.
- V. Claims 1-2, 9-15, 24 wherein Z in the bicyclic compound is NR1 completing a 5-membered carbocycle.

The inventions are distinct, each from the other because of the following reasons:

In view of PCT priority unity of invention exists only with certain categories of invention as set forth in PCT Rule 13. Note that compounds, corresponding compositions, and method of use and a process of making are considered to form a single, inventive concept as required by PCT Rule 13.1, 37 CFR 1.475 (d). Each group as outlined above are not so linked as they would require separate searches in the prior art and would be expected to raise different issues of novelty or inventive step. Further, compounds of Groups I-V together do not belong to a "recognized class of chemical compounds in the art" since there is no expectation in the art that members of all five groups behave in the same way in the context of the claimed invention's pharmacological activity, which is inherently unpredictable.